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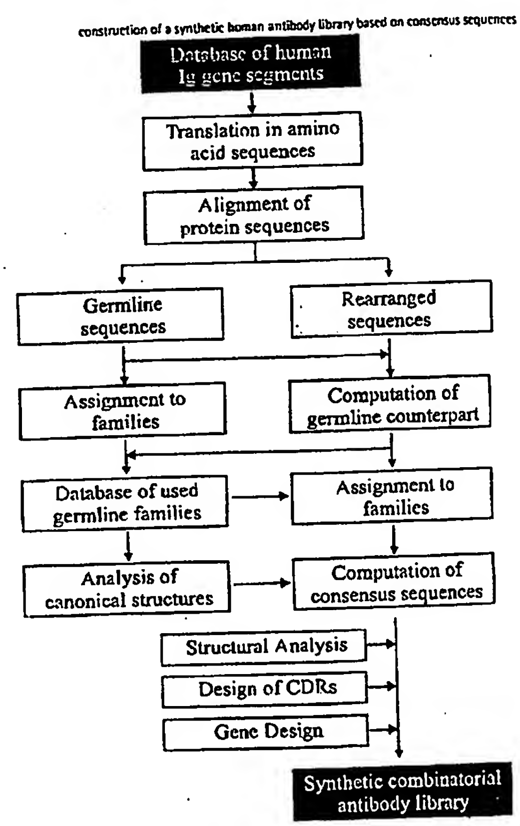
(57) Abstract

The present invention relates to synthetic DNA sequences which encode one or more collections of homologous proteins/(poly)peptides, and methods for generating and applying libraries of these DNA sequences. In particular, the invention relates to the preparation of a library of human-derived antibody genes by the use of synthetic consensus sequences which cover the structural repertoire of antibodies encoded in the human genome. Furthermore, the invention relates to the use of a single consensus antibody gene as a universal framework for highly diverse antibody libraries.



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Protein/(Poly)peptide Libraries

Field of the Invention

The present invention relates to synthetic DNA sequences which encode one or more collections of homologous proteins/(poly)peptides, and methods for generating and applying libraries of these DNA sequences. In particular, the invention relates to the preparation of a library of human-derived antibody genes by the use of synthetic consensus sequences which cover the structural repertoire of antibodies encoded in the human genome. Furthermore, the invention relates to the use of a single consensus antibody gene as a universal framework for highly diverse antibody libraries.

Background to the Invention

All current recombinant methods which use libraries of proteins/(poly)peptides, e.g. antibodies, to screen for members with desired properties, e.g. binding a given ligand, do not provide the possibility to improve the desired properties of the members in an easy and rapid manner. Usually a library is created either by inserting a random oligonucleotide sequence into one or more DNA sequences cloned from an organism, or a family of DNA sequences is cloned and used as the library. The library is then screened, e.g. using phage display, for members which show the desired property. The sequences of one or more of these resulting molecules are then determined. There is no general procedure available to improve these molecules further on.

Winter (EP 0 368 684 B1) has provided a method for amplifying (by PCR), cloning, and expressing antibody variable region genes. Starting with these genes he was able to create libraries of functional antibody fragments by randomizing the CDR3 of the heavy and/or the light chain. This process is functionally equivalent to the natural process of VJ and VDJ recombination which occurs during the development of B-cells in the immune system.

However the Winter invention does not provide a method for optimizing the binding affinities of antibody fragments further on, a process which would be functionally equivalent to the naturally occurring phenomenon of "affinity maturation", which is provided by the present invention. Furthermore, the Winter invention does not provide for artificial variable region genes, which represent a whole family of

structurally similar natural genes, and which can be assembled from synthetic DNA oligonucleotides. Additionally, Winter does not enable the combinatorial assembly of portions of antibody variable regions, a feature which is provided by the present invention. Furthermore, this approach has the disadvantage that the genes of all antibodies obtained in the screening procedure have to be completely sequenced, since, except for the PCR priming regions, no additional sequence information about the library members is available. This is time and labor intensive and potentially leads to sequencing errors.

The teaching of Winter as well as other approaches have tried to create large antibody libraries having high diversity in the complementarity determining regions (CDRs) as well as in the frameworks to be able to find antibodies against as many different antigens as possible. It has been suggested that a single universal framework may be useful to build antibody libraries, but no approach has yet been successful.

Another problem lies in the production of reagents derived from antibodies. Small antibody fragments show exciting promise for use as therapeutic agents, diagnostic reagents, and for biochemical research. Thus, they are needed in large amounts, and the expression of antibody fragments, e.g. Fv, single-chain Fv (scFv), or Fab in the periplasm of E. coli (Skerra & Plückthun, 1988; Better et al., 1988) is now used routinely in many laboratories. Expression yields vary widely, however. While some fragments yield up to several mg of functional, soluble protein per liter and OD of culture broth in shake flask culture (Carter et al., 1992, Plückthun et al. 1996), other fragments may almost exclusively lead to insoluble material, often found in so-called inclusion bodies. Functional protein may be obtained from the latter in modest yields by a laborious and time-consuming refolding process. The factors influencing antibody expression levels are still only poorly understood. Folding efficiency and stability of the antibody fragments, protease lability and toxicity of the expressed proteins to the host cells often severely limit actual production levels, and several attempts have been tried to increase expression yields. For example, Knappik & Plückthun (1995) could show that expression yield depends on the antibody sequence. They identified key residues in the antibody framework which influence expression yields dramatically. Similarly, Ullrich et al. (1995) found that point mutations in the CDRs can increase the yields in periplasmic antibody fragment expression. Nevertheless, these strategies are only applicable to a few antibodies. Since the Winter invention uses existing repertoires of antibodies, no influence on expressibility of the genes is possible.

Furthermore, the findings of Knappik & Plückthun and Ullrich demonstrate that the knowledge about antibodies, especially about folding and expression is still increasing. The Winter invention does not allow to incorporate such improvements into the library design.

The expressibility of the genes is important for the library quality as well, since the screening procedure relies in most cases on the display of the gene product on a phage surface, and efficient display relies on at least moderate expression of the gene.

These disadvantages of the existing methodologies are overcome by the present invention, which is applicable for all collections of homologous proteins. It has the following novel and useful features illustrated in the following by antibodies as an example:

Artificial antibodies and fragments thereof can be constructed based on known antibody sequences, which reflect the structural properties of a whole group of homologous antibody genes. Therefore it is possible to reduce the number of different genes without any loss in the structural repertoire. This approach leads to a limited set of artificial genes, which can be synthesized de novo, thereby allowing introduction of cleavage sites and removing unwanted cleavages sites. Furthermore, this approach enables (i), adapting the codon usage of the genes to that of highly expressed genes in any desired host cell and (ii), analyzing all possible pairs of antibody light (L) and heavy (H) chains in terms of interaction preference, antigen preference or recombinant expression titer, which is virtually impossible using the complete collection of antibody genes of an organism and all combinations thereof.

The use of a limited set of completely synthetic genes makes it possible to create cleavage sites at the boundaries of encoded structural sub-elements. Therefore, each gene is built up from modules which represent structural sub-elements on the protein/(poly)peptide level. In the case of antibodies, the modules consist of "framework" and "CDR" modules. By creating separate framework and CDR modules, different combinatorial assembly possibilities are enabled. Moreover, if two or more artificial genes carry identical pairs of cleavage sites at the boundaries of each of the genetic sub-elements, pre-built libraries of sub-elements can be inserted in these genes simultaneously, without any additional information related to any particular gene sequence. This strategy enables rapid optimization of, for example, antibody affinity, since DNA cassettes encoding libraries of genetic sub-elements can be (i), pre-built, stored and reused and (ii), inserted in any of these

sequences at the right position without knowing the actual sequence or having to determine the sequence of the individual library member.

Additionally, new information about amino acid residues important for binding, stability, or solubility and expression could be integrated into the library design by replacing existing modules with modules modified according to the new observations.

The limited number of consensus sequences used for creating the library allows to speed up the identification of binding antibodies after screening. After having identified the underlying consensus gene sequence, which could be done by sequencing or by using fingerprint restriction sites, just those part(s) comprising the random sequence(s) have to be determined. This reduces the probability of sequencing errors and of false-positive results.

The above mentioned cleavage sites can be used only if they are unique in the vector system where the artificial genes have been inserted. As a result, the vector has to be modified to contain none of these cleavage sites. The construction of a vector consisting of basic elements like resistance gene and origin of replication, where cleavage sites have been removed, is of general interest for many cloning attempts. Additionally, these vector(s) could be part of a kit comprising the above mentioned artificial genes and pre-built libraries.

The collection of artificial genes can be used for a rapid humanization procedure of non-human antibodies, preferably of rodent antibodies. First, the amino acid sequence of the non-human, preferably rodent antibody is compared with the amino acid sequences encoded by the collection of artificial genes to determine the most homologous light and heavy framework regions. These genes are then used for insertion of the genetic sub-elements encoding the CDRs of the non-human, preferably rodent antibody.

Surprisingly, it has been found that with a combination of only one consensus sequence for each of the light and heavy chains of a scFv fragment an antibody repertoire could be created yielding antibodies against virtually every antigen. Therefore, one aspect of the present invention is the use of a single consensus sequence as a universal framework for the creation of useful (poly)peptide libraries and antibody consensus sequences useful therefor.

Detailed Description of the Invention

The present invention enables the creation of useful libraries of (poly)peptides. In a first embodiment, the invention provides for a method of setting up nucleic acid sequences suitable for the creation of said libraries. In a first step, a collection of at least three homologous proteins is identified and then analyzed. Therefore, a database of the protein sequences is established where the protein sequences are aligned to each other. The database is used to define subgroups of protein sequences which show a high degree of similarity in both the sequence and, if information is available, in the structural arrangement. For each of the subgroups a (poly)peptide sequence comprising at least one consensus sequence is deduced which represents the members of this subgroup; the complete collection of (poly)peptide sequences represent therefore the complete structural repertoire of the collection of homologous proteins. These artificial (poly)peptide sequences are then analyzed, if possible, according to their structural properties to identify unfavorable interactions between amino acids within said (poly)peptide sequences or between said or other (poly)peptide sequences, for example, in multimeric proteins. Such interactions are then removed by changing the consensus sequence accordingly. The (poly)peptide sequences are then analyzed to identify sub-elements such as domains, loops, helices or CDRs. The amino acid sequence is backtranslated into a corresponding coding nucleic acid sequence which is adapted to the codon usage of the host planned for expressing said nucleic acid sequences. A set of cleavage sites is set up in a way that each of the sub-sequences encoding the sub-elements identified as described above, is flanked by two sites which do not occur a second time within the nucleic acid sequence. This can be achieved by either identifying a cleavage site already flanking a sub-sequence of by changing one or more nucleotides to create the cleavage site, and by removing that site from the remaining part of the gene. The cleavage sites should be common to all corresponding sub-elements or sub-sequences, thus creating a fully modular arrangement of the sub-sequences in the nucleic acid sequence and of the sub-elements in the corresponding (poly)peptide.

In a further embodiment, the invention provides for a method which sets up two or more sets of (poly)peptides, where for each set the method as described above is performed, and where the cleavage sites are not only unique within each set but also between any two sets. This method can be applied for the creation of (poly)peptide libraries comprising for example two α-helical domains from two different proteins, where said library is screened for novel hetero-association domains.

In yet a further embodiment, at least two of the sets as described above, are derived from the same collection of proteins or at least a part of it. This describes libraries comprising for example, but not limited to, two domains from antibodies such as VH and VL, or two extracellular loops of transmembrane receptors.

In another embodiment, the nucleic acid sequences set up as described above, are synthesized. This can be achieved by any one of several methods well known to the practitioner skilled in the art, for example, by total gene synthesis or by PCR-based approaches.

In one embodiment, the nucleic acid sequences are cloned into a vector. The vector could be a sequencing vector, an expression vector or a display (e.g. phage display) vector, which are well known to those skilled in the art. Any vector could comprise one nucleic acid sequence, or two or more nucleic sequences, either in different or the same operon. In the last case, they could either be cloned separately or as contiguous sequences.

In one embodiment, the removal of unfavorable interactions as described above, leads to enhanced expression of the modified (poly)peptides.

In a preferred embodiment, one or more sub-sequences of the nucleic acid sequences are replaced by different sequences. This can be achieved by excising the sub-sequences using the conditions suitable for cleaving the cleavage sites adjacent to or at the end of the sub-sequence, for example, by using a restriction enzyme at the corresponding restriction site under the conditions well known to those skilled in the art, and replacing the sub-sequence by a different sequence compatible with the cleaved nucleic acid sequence. In a further preferred embodiment, the different sequences replacing the initial sub-sequence(s) are genomic or rearranged genomic sequences, for example in grafting CDRs from non-human antibodies onto consensus antibody sequences for rapid humanization of non-human antibodies. In the most preferred embodiment, the different sequences are random sequences, thus replacing the sub-sequence by a collection of sequences to introduce variability and to create a library. The random sequences can be assembled in various ways, for example by using a mixture of mononucleotides or preferably a mixture of trinucleotides (Virnekäs et al., 1994) during automated oligonucleotide synthesis, by error-prone PCR or by other methods well known to the practitioner in the art. The random sequences may be completely randomized or biased towards or against certain codons according to

the amino acid distribution at certain positions in known protein sequences. Additionally, the collection of random sub-sequences may comprise different numbers of codons, giving rise to a collection of sub-elements having different lengths.

In another embodiment, the invention provides for the expression of the nucleic acid sequences from a suitable vector and under suitable conditions well known to those skilled in the art.

In a further preferred embodiment, the (poly)peptides expressed from said nucleic acid sequences are screened and, optionally, optimized. Screening may be performed by using one of the methods well known to the practitioner in the art, such as phage-display, selectively infective phage, polysome technology to screen for binding, assay systems for enzymatic activity or protein stability. (Poly)peptides having the desired property can be identified by sequencing of the corresponding nucleic acid sequence or by amino acid sequencing or mass spectrometry. In the case of subsequent optimization, the nucleic acid sequences encoding the initially selected (poly)peptides can optionally be used without sequencing. Optimization is performed by repeating the replacement of sub-sequences by different sequences, preferably by random sequences, and the screening step one or more times.

The desired property the (poly)peptides are screened for is preferably, but not exclusively, selected from the group of optimized affinity or specificity for a target molecule, optimized enzymatic activity, optimized expression yields, optimized stability and optimized solubility.

In one embodiment, the cleavage sites flanking the sub-sequences are sites recognized and cleaved by restriction enzymes, with recognition and cleavage sequences being either identical or different, the restricted sites either having blunt or sticky ends.

The length of the sub-elements is preferably, but not exclusively ranging between 1 amino acid, such as one residue in the active site of an enzyme or a structure-determining residue, and 150 amino acids, as for whole protein domains. Most preferably, the length ranges between 3 and 25 amino acids, such as most commonly found in CDR loops of antibodies.

The nucleic acid sequences could be RNA or, preferably, DNA.

In one embodiment, the (poly)peptides have an amino acid pattern characteristic of a particular species. This can for example be achieved by deducing the consensus sequences from a collection of homologous proteins of just one species, most preferably from a collection of human proteins. Since the (poly)peptides comprising consensus sequences are artificial, they have to be compared to the protein sequence(s) having the closest similarity to ensure the presence of said characteristic amino acid pattern.

In one embodiment, the invention provides for the creation of libraries of (poly)peptides comprising at least part of members or derivatives of the immunoglobulin superfamily, preferably of member or derivatives of the immnoglobulins. Most preferably, the invention provides for the creation of libraries of human antibodies, wherein said (poly)peptides are or are derived from heavy or light chain variable regions wherein said structural sub-elements are framework regions (FR) 1, 2, 3, or 4 or complementary determining regions (CDR) 1, 2, or 3. In a first step, a database of published antibody sequences of human origin is established where the antibody sequences are aligned to each other. The database is used to define subgroups of antibody sequences which show a high degree of similarity in both the sequence and the canonical fold of CDR loops (as determined by analysis of antibody structures). For each of the subgroups a consensus sequence is deduced which represents the members of this subgroup; the complete collection of consensus sequences represent therefore the complete structural repertoire of human antibodies.
These artificial genes are then constructed e.g. by total gene synthesis or by the use of synthetic genetic subunits. These genetic subunits correspond to structural sub-elements on the (poly)peptide level. On the DNA level, these genetic subunits are defined by cleavage sites at the start and the end of each of the sub-elements, which are unique in the vector system. All genes which are members of the collection of consensus sequences are constructed such that they contain a similar pattern of corresponding genetic sub-sequences. Most preferably, said (poly)peptides are or are derived from the HuCAL consensus genes: Vκ1, Vκ2, Vκ3, Vκ4, Vλ1, Vλ2, Vλ3, VH1A, VH1B, VH2, VH3, VH4, VH5, VH6, Cκ, Cλ, CH1 or any combination of said HuCAL consensus genes.
This collection of DNA molecules can then be used to create libraries of antibodies or antibody fragments, preferably Fv, disulphide-linked Fv, single-chain Fv (scFv), or Fab fragments, which may be used as sources of specificities against new target antigens. Moreover, the affinity of the antibodies can be optimized using pre-built library cassettes and a general procedure. The invention provides a method for identifying one or more genes encoding one or more antibody fragments which

binds to a target, comprising the steps of expressing the antibody fragments, and then screening them to isolate one or more antibody fragments which bind to a given target molecule. Preferably, an scFv fragment library comprising the combination of HuCAL VH3 and HuCAL Vλ2 consensus genes and at least a random sub-sequence encoding the heavy chain CDR3 sub-element is screened for binding antibodies. If necessary, the modular design of the genes can then be used to excise from the genes encoding the antibody fragments one or more genetic sub-sequences encoding structural sub-elements, and replacing them by one or more second sub-sequences encoding structural sub-elements. The expression and screening steps can then be repeated until an antibody having the desired affinity is generated.

Particularly preferred is a method in which one or more of the genetic subunits (e.g. the CDRs) are replaced by a random collection of sequences (the library) using the said cleavage sites. Since these cleavage sites are (i) unique in the vector system and (ii) common to all consensus genes, the same (pre-built) library can be inserted into all artificial antibody genes. The resulting library is then screened against any chosen antigen. Binding antibodies are selected, collected and used as starting material for the next library. Here, one or more of the remaining genetic subunits are randomized as described above.

A further embodiment of the present invention relates to fusion proteins by providing for a DNA sequence which encodes both the (poly)peptide, as described above, as well as an additional moiety. Particularly preferred are moieties which have a useful therapeutic function. For example, the additional moiety may be a toxin molecule which is able to kill cells (Vitetta et al., 1993). There are numerous examples of such toxins, well known to the one skilled in the art, such as the bacterial toxins Pseudomonas exotoxin A, and diphtheria toxin, as well as the plant toxins ricin, abrin, modeccin, saporin, and gelonin. By fusing such a toxin for example to an antibody fragment, the toxin can be targeted to, for example, diseased cells, and thereby have a beneficial therapeutic effect. Alternatively, the additional moiety may be a cytokine, such as IL-2 (Rosenberg & Lotze, 1986), which has a particular effect (in this case a T-cell proliferative effect) on a family of cells. In a further embodiment, the additional moiety may confer on its (poly)peptide partner a means of detection and/or purification. For example, the fusion protein could comprise the modified antibody fragment and an enzyme commonly used for detection purposes, such as alkaline phosphatase (Blake et al., 1984). There are numerous other moieties which can be used as detection or purification tags, which are well known to the practitioner skilled in the art. Particularly preferred are peptides comprising at least five histidine residues (Hochuli et al., 1988), which are able to bind to metal ions,

and can therefore be used for the purification of the protein to which they are fused (Lindner et al., 1992). Also provided for by the invention are additional moieties such as the commonly used C-myc and FLAG tags (Hopp et al., 1988; Knappik & Plückthun, 1994).

By engineering one or more fused additional domains, antibody fragments or any other (poly)peptide can be assembled into larger molecules which also fall under the scope of the present invention. For example, mini-antibodies (Pack, 1994) are dimers comprising two antibody fragments, each fused to a self-associating dimerization domain. Dimerization domains which are particularly preferred include those derived from a leucine zipper (Pack & Plückthun, 1992) or helix-turn-helix motif (Pack et al., 1993).

All of the above embodiments of the present invention can be effected using standard techniques of molecular biology known to anyone skilled in the art.

In a further embodiment, the random collection of sub-sequences (the library) is inserted into a singular nucleic acid sequence encoding one (poly)peptide, thus creating a (poly)peptide library based on one universal framework. Preferably a random collection of CDR sub-sequences is inserted into a universal antibody framework, for example into the HuCAL H3κ2 single-chain Fv fragment described above.

In further embodiments, the invention provides for nucleic acid sequence(s), vector(s) containing the nucleic acid sequence(s), host cell(s) containing the vector(s), and (poly)peptides, obtainable according to the methods described above.

In a further preferred embodiment, the invention provides for modular vector systems being compatible with the modular nucleic acid sequences encoding the (poly)peptides. The modules of the vectors are flanked by restriction sites unique within the vector system and essentially unique with respect to the restriction sites incorporated into the nucleic acid sequences encoding the (poly)peptides, except for example the restriction sites necessary for cloning the nucleic acid sequences into the vector. The list of vector modules comprises origins of single-stranded replication, origins of double-stranded replication for high- and low copy number plasmids, promotor/operator, repressor or terminator elements, resistance genes, potential recombination sites, gene III for display on filamentous phages, signal sequences, purification and detection tags, and sequences of additional moieties.

The vectors are preferably, but not exclusively, expression vectors or vectors suitable for expression and screening of libraries.

In another embodiment, the invention provides for a kit, comprising one or more of the list of nucleic acid sequence(s), recombinant vector(s), (poly)peptide(s), and vector(s) according to the methods described above, and suitable host cell(s) for producing the (poly)peptide(s).

In a preferred embodiment, the invention provides for the creation of libraries of human antibodies. In a first step, a database of published antibody sequences of human origin is established. The database is used to define subgroups of antibody sequences which show a high degree of similarity in both the sequence and the canonical fold (as determined by analysis of antibody structures). For each of the subgroups a consensus sequence is deduced which represents the members of this subgroup; the complete collection of consensus sequences represent therefore the complete structural repertoire of human antibodies.

These artificial genes are then constructed by the use of synthetic genetic subunits. These genetic subunits correspond to structural sub-elements on the protein level. On the DNA level, these genetic subunits are defined by cleavage sites at the start and the end of each of the subelements, which are unique in the vector system. All genes which are members of the collection of consensus sequences are constructed such that they contain a similar pattern of said genetic subunits.

This collection of DNA molecules can then be used to create libraries of antibodies which may be used as sources of specificities against new target antigens. Moreover, the affinity of the antibodies can be optimised using pre-built library cassettes and a general procedure. The invention provides a method for identifying one or more genes encoding one or more antibody fragments which binds to a target, comprising the steps of expressing the antibody fragments, and then screening them to isolate one or more antibody fragments which bind to a given target molecule. If necessary, the modular design of the genes can then be used to excise from the genes encoding the antibody fragments one or more genetic sub-sequences encoding structural sub-elements, and replacing them by one or more second sub-sequences encoding structural sub-elements. The expression and screening steps can then be repeated until an antibody having the desired affinity is generated.

Particularly preferred is a method in which one or more of the genetic subunits (e.g. the CDR's) are replaced by a random collection of sequences (the library) using the said cleavage sites. Since these cleavage sites are (i) unique in the vector system and (ii) common to all consensus genes, the same (pre-built) library can be inserted into all artificial antibody genes. The resulting library is then screened against any chosen antigen. Binding antibodies are eluted, collected and used as starting material for the next library. Here, one or more of the remaining genetic subunits are randomised as described above.

Definitions

Protein:
The term protein comprises monomeric polypeptide chains as well as homo- or heteromultimeric complexes of two or more polypeptide chains connected either by covalent interactions (such as disulphide bonds) or by non-covalent interactions (such as hydrophobic or electrostatic interactions).

Analysis of homologous proteins:
The amino acid sequences of three or more proteins are aligned to each other (allowing for introduction of gaps) in a way which maximizes the correspondence between identical or similar amino acid residues at all positions. These aligned sequences are termed homologous if the percentage of the sum of identical and/or similar residues exceeds a defined threshold. This threshold is commonly regarded by those skilled in the art as being exceeded when at least 15% of the amino acids in the aligned genes are identical, and at least 30% are similar. Examples for families of homologous proteins are: immunoglobulin superfamily, scavenger receptor superfamily, fibronectin superfamilies (e.g. type II and III), complement control protein superfamily, cytokine receptor superfamily, cystine knot proteins, tyrosine kinases, and numerous other examples well known to one of ordinary skill in the art.

Consensus sequence:
Using a matrix of at least three aligned amino acid sequences, and allowing for gaps in the alignment, it is possible to determine the most frequent amino acid residue at each position. The consensus sequence is that sequence which comprises the amino acids which are most frequently represented at each position. In the event that two or more amino acids are equally represented at a single position, the consensus sequence includes both or all of those amino acids.

Removing unfavorable interactions:
The consensus sequence is per se in most cases artificial and has to be analyzed in order to change amino acid residues which, for example, would prevent the resulting molecule to adapt a functional tertiary structure or which would block the interaction with other (poly)peptide chains in multimeric complexes. This can be done either by (i) building a three-dimensional model of the consensus sequence using known related structures as a template, and identifying amino acid residues within the model which may interact unfavorably with each other, or (ii) analyzing the matrix of aligned amino acid sequences in order to detect combinations of amino

acid residues within the sequences which frequently occur together in one sequence and are therefore likely to interact with each other. These probable interaction-pairs are then tabulated and the consensus is compared with these "interaction maps". Missing or wrong interactions in the consensus are repaired accordingly by introducing appropriate changes in amino acids which minimize unfavorable interactions.

Identification of structural sub-elements:

Structural sub-elements are stretches of amino acid residues within a protein/(poly)peptide which correspond to a defined structural or functional part of the molecule. These can be loops (e.g. CDR loops of an antibody) or any other secondary or functional structure within the protein/(poly)peptide (domains, α-helices, ß-sheets, framework regions of antibodies, etc.). A structural sub-element can be identified using known structures of similar or homologous (poly)peptides; or by using the above mentioned matrices of aligned amino acid sequences. Here the variability at each position is the basis for determining stretches of amino acid residues which belong to a structural sub-element (e.g. hypervariable regions of an antibody).

Sub-sequence:

A sub-sequence is defined as a genetic module which is flanked by unique cleavage sites and encodes at least one structural sub-element. It is not necessarily identical to a structural sub-element.

Cleavage site:

A short DNA sequence which is used as a specific target for a reagent which cleaves DNA in a sequence-specific manner (e.g. restriction endonucleases).

Compatible cleavage sites:

Cleavage sites are compatible with each other, if they can be efficiently ligated without modification and, preferably, also without adding an adapter molecule..

Unique cleavage sites:

A cleavage site is defined as unique if it occurs only once in a vector containing at least one of the genes of interest, or if a vector containing at least one of the genes of interest could be treated in a way that only one of the cleavage sites could be used by the cleaving agent.

Corresponding (poly)peptide sequences:
Sequences deduced from the same part of one group of homologous proteins are called corresponding (poly)peptide sequences.

Common cleavage sites:
A cleavage site in at least two corresponding sequences, which occurs at the same functional position (i.e. which flanks a defined sub-sequence), which can be hydrolyzed by the same cleavage tool and which yields identical compatible ends is termed a common cleavage site.

Excising genetic sub-sequences:
A method which uses the unique cleavage sites and the corresponding cleavage reagents to cleave the target DNA at the specified positions in order to isolate, remove or replace the genetic sub-sequence flanked by these unique cleavage sites.

Exchanging genetic sub-sequences:
A method by which an existing sub-sequence is removed using the flanking cleavage sites of this sub-sequence, and a new sub-sequence or a collection of sub-sequences, which contain ends compatible with the cleavage sites thus created, is inserted.

Expression of genes:
The term expression refers to in vivo or in vitro processes, by which the information of a gene is transcribed into mRNA and then translated into a protein/(poly)peptide. Thus, the term expression refers to a process which occurs inside cells, by which the information of a gene is transcribed into mRNA and then into a protein. The term expression also includes all events of post-translational modification and transport, which are necessary for the (poly)peptide to be functional.

Screening of protein/(poly)peptide libraries:
Any method which allows isolation of one or more proteins/(poly)peptides having a desired property from other proteins/(poly)peptides within a library.

Amino acid pattern characteristic for a species:
A (poly)peptide sequence is assumed to exhibit an amino acid pattern characteristic for a species if it is deduced from a collection of homologous proteins from just this species.

Immunoglobulin superfamily (IgSF):

The IgSF is a family of proteins comprising domains being characterized by the immunoglobulin fold. The IgSF comprises for example T-cell receptors and the immunoglobulins (antibodies).

Antibody framework:

A framework of an antibody variable domain is defined by Kabat et al. (1991) as the part of the variable domain which serves as a scaffold for the antigen binding loops of this variable domain.

Antibody CDR:

The CDRs (complementarity determining regions) of an antibody consist of the antigen binding loops, as defined by Kabat et al. (1991). Each of the two variable domains of an antibody Fv fragment contain three CDRs.

HuCAL:

Acronym for Human Combinatorial Antibody Library. Antibody Library based on modular consensus genes according to the invention (see Example 1).

Antibody fragment:

Any portion of an antibody which has a particular function, e.g. binding of antigen. Usually, antibody fragments are smaller than whole antibodies. Examples are Fv, disulphide-linked Fv, single-chain Fv (scFv), or Fab fragments. Additionally, antibody fragments are often engineered to include new functions or properties.

Universal framework:

One single framework which can be used to create the full variability of functions, specificities or properties which is originally sustained by a large collection of different frameworks, is called universal framework.

Binding of an antibody to its target:

The process which leads to a tight and specific association between an antibody and a corresponding molecule or ligand is called binding. A molecule or ligand or any part of a molecukle or ligand which is recognized by an antibody is called the target.

Replacing genetic sub-sequences

A method by which an existing sub-sequence is removed using the flanking cleavage sites of this sub-sequence, and a new sub-sequence or collection of sub-

sequences, which contains ends compatible with the cleavage sites thus created, is inserted.

Assembling of genetic sequences:

Any process which is used to combine synthetic or natural genetic sequences in a specific manner in order to get longer genetic sequences which contain at least parts of the used synthetic or natural genetic sequences.

Analysis of homologous genes:

The corresponding amino acid sequences of two or more genes are aligned to each other in a way which maximizes the correspondence between identical or similar amino acid residues at all positions. These aligned sequences are termed homologous if the percentage of the sum of identical and/or similar residues exceeds a defined threshold. This threshold is commonly regarded by those skilled in the art as being exceeded when at least 15 per cent of the amino acids in the aligned genes are identical, and at least 30 per cent are similar.

Legends to Figures and Tables

Fig. 1: Flow chart outlining the process of construction of a synthetic human antibody library based on consensus sequences.

Fig. 2: Alignment of consensus sequences designed for each subgroup (amino acid residues are shown with their standard one-letter abbreviation). (**A**) kappa sequences, (**B**) lambda sequences and (**C**), heavy chain sequences. The positions are numbered according to Kabat (1991). In order to maximize homology in the alignment, gaps (—) have been introduced in the sequence at certain positions.

Fig. 3: Gene sequences of the synthetic V kappa consensus genes. The corresponding amino acid sequences (see Fig. 2) as well as the unique cleavage sites are also shown.

Fig. 4: Gene sequences of the synthetic V lambda consensus genes. The corresponding amino acid sequences (see Fig. 2) as well as the unique cleavage sites are also shown.

Fig. 5: Gene sequences of the synthetic V heavy chain consensus genes. The corresponding amino acid sequences (see Fig. 2) as well as the unique cleavage sites are also shown.

Fig. 6: Oligonucleotides used for construction of the consensus genes. The oligos are named according to the corresponding consensus gene, e.g. the gene Vκ1 was constructed using the six oligonucleotides O1K1 to O1K6. The oligonucleotides used for synthesizing the genes encoding the constant domains Cκ (OCLK1 to 8) and CH1 (OCH1 to 8) are also shown.

Fig. 7 A/B: Sequences of the synthetic genes encoding the constant domains Cκ (A) and CH1 (B). The corresponding amino acid sequences as well as unique cleavage sites introduced in these genes are also shown.

Fig. 7C: Functional map and sequence of module M24 comprising the synthetic Cλ gene segment (huCL lambda).

Fig. 7D: Oligonucleotides used for synthesis of module M24.

Fig. 8: Sequence and restriction map of the synthetic gene encoding the consensus single-chain fragment VH3-Vκ2. The signal sequence (amino acids 1 to 21) was derived from the *E. coli* phoA gene (Skerra &

Plückthun, 1988). Between the phoA signal sequence and the VH3 domain, a short sequence stretch encoding 4 amino acid residues (amino acid 22 to 25) has been inserted in order to allow detection of the single-chain fragment in Western blot or ELISA using the monoclonal antibody M1 (Knappik & Plückthun, 1994). The last 6 basepairs of the sequence were introduced for cloning purposes (EcoRI site).

Fig. 9: Plasmid map of the vector pIG10.3 used for phage display of the H3κ2 scFv fragment. The vector is derived from pIG10 and contains the gene for the lac operon repressor, lacI, the artificial operon encoding the H3κ2-gene3ss fusion under control of the lac promoter, the lpp terminator of transcription, the single-strand replication origin of the *E. coli* phage f1 (F1_ORI), a gene encoding β-lactamase (bla) and the ColEI derived origin of replication.

Fig. 10: Sequencing results of independent clones from the initial library, translated into the corresponding amino acid sequences. (**A**) Amino acid sequence of the VH3 consensus heavy chain CDR3 (position 93 to 102, Kabat numbering). (**B**) Amino acid sequences of 12 clones of the 10-mer library. (**C**) Amino acid sequences of 11 clones of the 15-mer library, *: single base deletion.

Fig. 11: Expression test of individual library members. (**A**) Expression of 9 independent clones of the 10-mer library. (**B**) Expression of 9 independent clones of the 15-mer library. The lane designated with M contains the size marker. Both the gp3-scFv fusion and the scFv monomer are indicated.

Fig. 12: Enrichment of specific phage antibodies during the panning against FITC-BSA. The initial as well as the subsequent fluorescein-specific sub-libraries were panned against the blocking buffer and the ratio of the phage eluted from the FITC-BSA coated well vs. that from the powder milk coated well from each panning round is presented as the „specificity factor".

Fig. 13: Phage ELISA of 24 independent clones after the third round of panning tested for binding on FITC-BSA.

Fig. 14: Competition ELISA of selected FITC-BSA binding clones. The ELISA signals (OD_{405nm}) of scFv binding without inhibition are taken as 100%.

Fig. 15: Sequencing results of the heavy chain CDR3s of independent clones after 3 rounds of panning against FITC-BSA, translated into the corresponding amino acid sequences (position 93 to 102. Kabat numbering).

Fig. 16: Coomassie-Blue stained SDS-PAGE of the purified anti-fluorescein scFv fragments: M: molecular weight marker, A: total soluble cell extract after induction, B: fraction of the flow-through, C, D and E: purified scFv fragments 1HA-3E4, 1HA-3E5 and 1HA-3E10, respectively.

Fig. 17: Enrichment of specific phage antibodies during the panning against ß-estradiol-BSA, testosterone-BSA, BSA, ESL-1, interleukin-2, lymphotoxin-ß, and LeY-BSA after three rounds of panning.

Fig. 18: ELISA of selected ESL-1 and ß-estradiol binding clones

Fig. 19: Selectivity and cross-reactivity of HuCAL antibodies: in the diagonal specific binding of HuCAL antibodies can be seen, off-diagonal signals show non-specific cross-reactivity.

Fig. 20: Sequencing results of the heavy chain CDR3s of independent clones after 3 rounds of panning against ß-estradiol-BSA, translated into the corresponding amino acid sequences (position 93 to 102, Kabat numbering). One clone is derived from the 10mer library.

Fig. 21: Sequencing results of the heavy chain CDR3s of independent clones after 3 rounds of panning against testosterone-BSA, translated into the corresponding amino acid sequences (position 93 to 102, Kabat numbering).

Fig. 22: Sequencing results of the heavy chain CDR3s of independent clones after 3 rounds of panning against lymphotoxin-ß, translated into the corresponding amino acid sequences (position 93 to 102, Kabat numbering). One clone comprises a 14mer CDR, presumably introduced by incomplete coupling of the trinucleotide mixture during oligonucleotide synthesis.

Fig. 23: Sequencing results of the heavy chain CDR3s of independent clones after 3 rounds of panning against ESL-1, translated into the corresponding amino acid sequences (position 93 to 102, Kabat numbering). Two clones are derived from the 10mer library. One clone comprises a 16mer CDR, presumably introduced by chain elongation during oligonucleotide synthesis using trinucleotides.

Fig. 24: Sequencing results of the heavy chain CDR3s of independent clones after 3 rounds of panning against BSA, translated into the corresponding amino acid sequences (position 93 to 102, Kabat numbering).

Fig. 25: Schematic representation of the modular pCAL vector system.

Fig. 25a: List of restriction sites already used in or suitable for the modular HuCAL genes and pCAL vector system.

Fig. 26: List of the modular vector elements for the pCAL vector series: shown are only those restriction sites which are part of the modular system.

Fig. 27: Functional map and sequence of the multi-cloning site module (MCS)

Fig. 28: Functional map and sequence of the pMCS cloning vector series.

Fig. 29: Functional map and sequence of the pCAL module M1 (see Fig. 26).

Fig. 30: Functional map and sequence of the pCAL module M7-III (see Fig. 26).

Fig. 31: Functional map and sequence of the pCAL module M9-II (see Fig. 26).

Fig. 32: Functional map and sequence of the pCAL module M11-II (see Fig. 26).

Fig. 33: Functional map and sequence of the pCAL module M14-Ext2 (see Fig. 26).

Fig. 34: Functional map and sequence of the pCAL module M17 (see Fig. 26).

Fig. 35: Functional map and sequence of the modular vector pCAL4.

Fig. 35a: Functional maps and sequences of additional pCAL modules (M2, M3, M7I, M7II, M8, M10II, M11II, M12, M13, M19, M20, M21, M41) and of low-copy number plasmid vectors (pCALO1 to pCALO3).

Fig. 35b: List of oligonucleotides and primers used for synthesis of pCAL vector modules.

Fig. 36: Functional map and sequence of the ß-lactamase cassette for replacement of CDRs for CDR library cloning.

Fig. 37: Oligo and primer design for Vκ CDR3 libraries

Fig. 38: Oligo and primer design for Vλ CDR3 libraries

Fig. 39: Functional map of the pBS13 expression vector series.

Fig. 40: Expression of all 49 HuCAL scFvs obtained by combining each of the 7 VH genes with each of the 7 VL genes (pBS13, 30°C): Values are given for the percentage of soluble vs. insoluble material, the total and the soluble amount compared to the combination H3κ2, which was set to 100%. In addition, the corresponding values for the McPC603 scFv are given.

Table 1: Summary of human immunoglobulin germline sequences used for computing the germline membership of rearranged sequences. (**A**) kappa sequences, (**B**) lambda sequences and (**C**), heavy chain sequences. (1) The germline name used in the various calculations, (2) the references number for the corresponding sequence (see appendix for sequence related citations), (3) the family where each sequence belongs to and (4), the various names found in literature for germline genes with identical amino acid sequences.

Table 2: Rearranged human sequences used for the calculation of consensus sequences. (**A**) kappa sequences, (**B**) lambda sequences and (**C**), heavy chain sequences. The table summarized the name of the sequence (1),

the length of the sequence in amino acids (2), the germline family (3) as well as the computed germline counterpart (4). The number of amino acid exchanges between the rearranged sequence and the germline sequence is tabulated in (5), and the percentage of different amino acids is given in (6). Column (7) gives the references number for the corresponding sequence (see appendix for sequence related citations).

Table 3: Assignment of rearranged V sequences to their germline counterparts. (A) kappa sequences, (B) lambda sequences and (C), heavy chain sequences. The germline genes are tabulated according to their family (1), and the number of rearranged genes found for every germline gene is given in (2).

Table 4: Computation of the consensus sequence of the rearranged V kappa sequences. (A), V kappa subgroup 1, (B), V kappa subgroup 2, (C), V kappa subgroup 3 and (D), V kappa subgroup 4. The number of each amino acid found at each position is tabulated together with the statistical analysis of the data. (1) Amino acids are given with their standard one-letter abbreviations (and B means D or N, Z means E or Q and X means any amino acid). The statistical analysis summarizes the number of sequences found at each position (2), the number of occurrences of the most common amino acid (3), the amino acid residue which is most common at this position (4), the relative frequency of the occurrence of the most common amino acid (5) and the number of different amino acids found at each position (6).

Table 5: Computation of the consensus sequence of the rearranged V lambda sequences. (A), V lambda subgroup 1, (B), V lambda subgroup 2, and (C), V lambda subgroup 3. The number of each amino acid found at each position is tabulated together with the statistical analysis of the data. Abbreviations are the same as in Table 4.

Table 6: Computation of the consensus sequence of the rearranged V heavy chain sequences. (A), V heavy chain subgroup 1A, (B), V heavy chain subgroup 1B, (C), V heavy chain subgroup 2, (D), V heavy chain subgroup 3, (E), V heavy chain subgroup 4, (F), V heavy chain subgroup 5, and (G), V heavy chain subgroup 6. The number of each amino acid found at each position is tabulated together with the statistical analysis of the data. Abbreviations are the same as in Table 4.

Examples

Example 1: Design of a Synthetic Human Combinatorial Antibody Library (HuCAL)

The following example describes the design of a fully synthetic human combinatorial antibody library (HuCAL), based on consensus sequences of the human immunoglobulin repertoire, and the synthesis of the consensus genes. The general procedure is outlined in Fig. 1.

1.1 Sequence database

1.1.1 Collection and alignment of human immunoglobulin sequences

In a first step, sequences of variable domains of human immunoglobulins have been collected and divided into three sub bases: V heavy chain (VH), V kappa (Vκ) and V lambda (Vλ). For each sequence, the gene sequence was then translated into the corresponding amino acid sequence. Subsequently, all amino acid sequences were aligned according to Kabat et al. (1991). In the case of Vλ sequences, the numbering system of Chuchana et al. (1990) was used. Each of the three main databases was then divided into two further sub bases: the first sub base contained all sequences derived from rearranged V genes, where more than 70 positions of the sequence were known. The second sub base contained all germline gene segments (without the D- and J- minigenes; pseudogenes with internal stop codons were also removed). In all cases, where germline sequences with identical amino acid sequence but different names were found, only one sequence was used (see Table 1). The final databases of rearranged sequences contained 386, 149 and 674 entries for Vκ, Vλ and VH, respectively. The final databases of germline sequences contained 48, 26 and 141 entries for Vκ, Vλ and VH, respectively.

1.1.2 Assignment of sequences to subgroups

The sequences in the three germline databases where then grouped according to sequence homology (see also Tomlinson et al., 1992, Williams & Winter, 1993, and Cox et al., 1994). In the case of Vκ, 7 families could be established. Vλ was divided into 8 families and VH into 6 families. The VH germline genes of the VH7 family (Van Dijk et al., 1993) were grouped into the VH1 family, since the genes of the two families are highly homologous. Each family contained different numbers of germline genes, varying from 1 (for example VH6) to 47 (VH3).

1.2 Analysis of sequences

1.2.1 Computation of germline membership

For each of the 1209 amino acid sequences in the databases of rearranged genes, the nearest germline counterpart, i.e. the germline sequence with the smallest number of amino acid differences was then calculated. After the germline counterpart was found, the number of somatic mutations which occurred in the rearranged gene and which led to amino acid exchanges could be tabulated. In 140 cases, the germline counterpart could not be calculated exactly, because more than one germline gene was found with an identical number of amino acid exchanges. These rearranged sequences were removed from the database. In a few cases, the number of amino acid exchanges was found to be unusually large (>20 for VL and >25 for VH), indicating either heavily mutated rearranged genes or derivation from germline genes not present in the database. Since it was not possible to distinguish between these two possibilities, these sequences were also removed from the database. Finally, 12 rearranged sequences were removed from the database because they were found to have very unusual CDR lengths and composition or unusual amino acids at canonical positions (see below). In summary, 1023 rearranged sequences out of 1209 (85%) could be clearly assigned to their germline counterparts (see Table 2).

After this calculation, every rearranged gene could be arranged in one of the families established for the germline genes. Now the usage of each germline gene, i.e. the number of rearranged genes which originate from each germline gene, could be calculated (see Table 2). It was found that the usage was strongly biased towards a subset of germline genes, whereas most of the germline genes were not present as rearranged genes in the database and therefore apparently not used in the immune system (Table 3). This observation had already been reported in the case of Vκ (Cox, et al., 1994). All germline gene families, where no or only very few rearranged counterparts could be assigned, were removed from the database, leaving 4 Vκ, 3 Vλ, and 6 VH families.

1.2.2 Analysis of CDR conformations

The conformation of the antigen binding loops of antibody molecules, the CDRs, is strongly dependent on both the length of the CDRs and the amino acid residues located at the so-called canonical positions (Chothia & Lesk, 1987). It has been found that only a few canonical structures exist, which determine the structural

repertoire of the immunoglobulin variable domains (Chothia et al., 1989). The canonical amino acid positions can be found in CDR as well as framework regions. The 13 used germline families defined above (7 VL and 6 VH) were now analyzed for their canonical structures in order to define the structural repertoire encoded in these families.

In 3 of the 4 Vκ families (Vκ1, 2 and 4), one different type of CDR1 conformation could be defined for every family. The family Vκ3 showed two types of CDR1 conformation: one type which was identical to Vκ1 and one type only found in Vκ3. All Vκ CDR2s used the same type of canonical structure. The CDR3 conformation is not encoded in the germline gene segments. Therefore, the 4 Vκ families defined by sequence homology and usage corresponded also to 4 types of canonical structures found in Vκ germline genes.

The 3 Vλ families defined above showed 3 types of CDR1 conformation, each family with one unique type. The Vλ1 family contained 2 different CDR1 lengths (13 and 14 amino acids), but identical canonical residues, and it is thought that both lengths adopt the same canonical conformation (Chothia & Lesk, 1987). In the CDR2 of the used Vλ germlines, only one canonical conformation exists, and the CDR3 conformation is not encoded in the germline gene segments. Therefore, the 3 Vλ families defined by sequence homology and usage corresponded also to 3 types of canonical structures.

The structural repertoire of the human VH sequences was analyzed in detail by Chothia et al., 1992. In total, 3 conformations of CDR1 (H1-1, H1-2 and H1-3) and 6 conformations of CDR2 (H2-1, H2-2, H2-3, H2-4, H2-5 and H2-x) could be defined. Since the CDR3 is encoded in the D- and J-minigene segments, no particular canonical residues are defined for this CDR.
All the members of the VH1 family defined above contained the CDR1 conformation H1-1, but differed in their CDR2 conformation: the H2-2 conformation was found in 6 germline genes, whereas the conformation H2-3 was found in 8 germline genes. Since the two types of CDR2 conformations are defined by different types of amino acid at the framework position 72, the VH1 family was divided into two subfamilies: VH1A with CDR2 conformation H2-2 and VH1B with the conformation H2-3. The members of the VH2 family all had the conformations H1-3 and H2-1 in CDR1 and CDR2, respectively. The CDR1 conformation of the VH3 members was found in all cases to be H1-1, but 4 different types were found in CDR2 (H2-1, H2-3, H2-4 and H2-x). In these CDR2 conformations, the canonical framework residue 71 is always

defined by an arginine. Therefore, it was not necessary to divide the VH3 family into subfamilies, since the 4 types of CDR2 conformations were defined solely by the CDR2 itself. The same was true for the VH4 family. Here, all 3 types of CDR1 conformations were found, but since the CDR1 conformation was defined by the CDR itself (the canonical framework residue 26 was found to be glycine in all cases), no subdivisions were necessary. The CDR2 conformation of the VH4 members was found to be H2-1 in all cases. All members of the VH5 family were found to have the conformation H1-1 and H2-2, respectively. The single germline gene of the VH6 family had the conformations H1-3 and H2-5 in CDR1 and CDR2, respectively.

In summary, all possible CDR conformations of the Vκ and Vλ genes were present in the 7 families defined by sequence comparison. From the 12 different CDR conformations found in the used VH germline genes, 7 could be covered by dividing the family VH1 into two subfamilies, thereby creating 7 VH families. The remaining 5 CDR conformations (3 in the VH3 and 2 in the VH4 family) were defined by the CDRs themselves and could be created during the construction of CDR libraries. Therefore, the structural repertoire of the used human V genes could be covered by 49 (7 x 7) different frameworks.

1.2.3 Computation of consensus sequences

The 14 databases of rearranged sequences (4 Vκ, 3 Vλ and 7 VH) were used to compute the HuCAL consensus sequences of each subgroup (4 HuCAL- Vκ, 3 HuCAL- Vλ, 7 HuCAL- VH, see Table 4, 5 and 6). This was done by counting the number of amino acid residues used at each position (position variability) and subsequently identifying the amino acid residue most frequently used at each position. By using the rearranged sequences instead of the used germline sequences for the calculation of the consensus, the consensus was weighted according to the frequency of usage. Additionally, frequently mutated and highly conserved positions could be identified. The consensus sequences were cross-checked with the consensus of the germline families to see whether the rearranged sequences were biased at certain positions towards amino acid residues which do not occur in the collected germline sequences, but this was found not to be the case. Subsequently, the number of differences of each of the 14 consensus sequences to each of the germline sequences found in each specific family was calculated. The overall deviation from the most homologous germline sequence was found to be 2.4 amino acid residues (s.d. = 2.7), ensuring that the "artificial" consensus sequences

can still be considered as truly human sequences as far as immunogenicity is concerned.

1.3 Structural analysis

So far, only sequence information was used to design the consensus sequences. Since it was possible that during the calculation certain artificial combinations of amino acid residues have been created, which are located far away in the sequence but have contacts to each other in the three dimensional structure, leading to destabilized or even misfolded frameworks, the 14 consensus sequences were analyzed according to their structural properties.

It was rationalized that all rearranged sequences present in the database correspond to functional and therefore correctly folded antibody molecules. Hence, the most homologous rearranged sequence was calculated for each consensus sequence. The positions where the consensus differed from the rearranged sequence were identified as potential "artificial residues" and inspected.

The inspection itself was done in two directions. First, the local sequence stretch around each potentially "artificial residue" was compared with the corresponding stretch of all the rearranged sequences. If this stretch was found to be truly artificial, i.e. never occurred in any of the rearranged sequences, the critical residue was converted into the second most common amino acid found at this position and analyzed again. Second, the potentially "artificial residues" were analyzed for their long range interactions. This was done by collecting all available structures of human antibody variable domains from the corresponding PDB files and calculating for every structure the number and type of interactions each amino acid residue established to each side-chain. These "interaction maps" were used to analyze the probable side-chain/side-chain interactions of the potentially "artificial residues". As a result of this analysis, the following residues were exchanged (given is the name of the gene, the position according to Kabat's numbering scheme, the amino acid found at this position as the most abundant one and the amino acid which was used instead):

VH2: $S_{65}T$
Vκ1: $N_{34}A$,
Vκ3: $G_{9}A$, $D_{60}A$, $R_{77}S$
Vλ3: $V_{78}T$

1.4 Design of CDR sequences

The process described above provided the complete consensus sequences derived solely from the databases of rearranged sequences. It was rationalized that the CDR1 and CDR2 regions should be taken from the databases of used germline sequences, since the CDRs of rearranged and mutated sequences are biased towards their particular antigens. Moreover, the germline CDR sequences are known to allow binding to a variety of antigens in the primary immune response, where only CDR3 is varied. Therefore, the consensus CDRs obtained from the calculations described above were replaced by germline CDRs in the case of VH and Vκ. In the case of Vλ, a few amino acid exchanges were introduced in some of the chosen germline CDRs in order to avoid possible protease cleavage sites as well as possible structural constraints.

The CDRs of following germline genes have been chosen:

HuCAL gene	CDR1	CDR2
HuCAL-VH1A	VH1-12-1	VH1-12-1
HuCAL-VH1B	VH1-13-16	VH1-13-6,-7,-8,-9
HuCAL-VH2	VH2-31-10,-11,-12,-13	VH2-31-3,-4
HuCAL-VH3	VH3-13-8,-9,-10	VH3-13-8,-9,-10
HuCAL-VH4	VH4-11-7 to -14	VH4-11-8,-9,-11,-12,-14,-16 VH4-31-17,-18,-19,-20
HuCAL-VH5	VH5-12-1,-2	VH5-12-1,-2
HuCAL-VH6	VH6-35-1	VH6-35-1
HuCAL-Vκ1	Vκ1-14,-15	Vκ1-2,-3,-4,-5,-7,-8,-12,-13,-18,-19
HuCAL-Vκ2	Vκ2-6	Vκ2-6
HuCAL-Vκ3	Vκ3-1,-4	Vκ3-4
HuCAL-Vκ4	Vκ4-1	Vκ4-1
HuCAL-Vλ1	HUMLV117,DPL5	DPL5
HuCAL-Vλ2	DPL11,DPL12	DPL12
HuCAL-Vλ3	DPL23	HUMLV318

In the case of the CDR3s, any sequence could be chosen since these CDRs were planned to be the first to be replaced by oligonucleotide libraries. In order to study the expression and folding behavior of the consensus sequences in *E. coli*, it would be useful to have all sequences with the same CDR3, since the influence of the CDR3s on the folding behavior would then be identical in all cases. The dummy sequences QQHYTTPP and ARWGGDGFYAMDY were selected for the VL chains (kappa and lambda) and for the VH chains, respectively. These sequences are known to be compatible with antibody folding in *E. coli* (Carter et al., 1992).

1.5 Gene design

The final outcome of the process described above was a collection of 14 HuCAL amino acid sequences, which represent the frequently used structural antibody repertoire of the human immune system (see Figure 2). These sequences were back-translated into DNA sequences. In a first step, the back-translation was done using only codons which are known to be frequently used in *E. coli*. These gene sequences were then used for creating a database of all possible restriction endonuclease sites, which could be introduced without changing the corresponding amino acid sequences. Using this database, cleavage sites were selected which were located at the flanking regions of all sub-elements of the genes (CDRs and framework regions) and which could be introduced in all HuCAL VH, Vκ or Vλ genes simultaneously at the same position. In a few cases it was not possible to find cleavage sites for all genes of a subgroup. When this happened, the amino acid sequence was changed, if this was possible according to the available sequence and structural information. This exchange was then analyzed again as described above. In total, the following 6 amino acid residues were exchanged during this design (given is the name of the gene, the position according to Kabat's numbering scheme, the amino acid found at this position as the most abundant one and the amino acid which was used instead):

VH2: T_3Q

VH6: $S_{42}G$

Vκ3: E_1D, $I_{58}V$

Vκ4: $K_{24}R$

Vλ3: $T_{22}S$

In one case (5'-end of VH framework 3) it was not possible to identify a single cleavage site for all 7 VH genes. Two different type of cleavage sites were used instead: BstEII for HuCAL VH1A, VH1B, VH4 and VH5, and NspV for HuCAL VH2, VH3, VH4 and VH6.

Several restriction endonuclease sites were identified, which were not located at the flanking regions of the sub-elements but which could be introduced in every gene of a given group without changing the amino acid sequence. These cleavage sites were also introduced in order to make the system more flexible for further improvements. Finally, all but one remaining restriction endonuclease sites were removed in every gene sequence. The single cleavage site, which was not removed was different in all genes of a subgroup and could be therefore used as a "fingerprint" site to ease the identification of the different genes by restriction digest. The designed genes, together with the corresponding amino acid sequences and the group-specific restriction endonuclease sites are shown in Figure 3, 4 and 5, respectively.

1.6 Gene synthesis and cloning

The consensus genes were synthesized using the method described by Prodromou & Pearl, 1992, using the oligonucleotides shown in Fig. 6. Gene segments encoding the human constant domains Cκ, Cλ and CH1 were also synthesized, based on sequence information given by Kabat et al., 1991 (see Fig. 6 and Fig. 7). Since for both the CDR3 and the framework 4 gene segments identical sequences were chosen in all HuCAL Vκ, Vλ and VH genes, respectively, this part was constructed only once, together with the corresponding gene segments encoding the constant domains. The PCR products were cloned into pCR-Script KS(+) (Stratagene, Inc.) or pZErO-1 (Invitrogen, Inc.) and verified by sequencing.

Example 2: Cloning and Testing of a HuCAL-Based Antibody Library

A combination of two of the synthetic consensus genes was chosen after construction to test whether binding antibody fragments can be isolated from a library based on these two consensus frameworks. The two genes were cloned as a single-chain Fv (scFv) fragment, and a VH-CDR3 library was inserted. In order to test the library for the presence of functional antibody molecules, a selection procedure

was carried out using the small hapten fluorescein bound to BSA (FITC-BSA) as antigen.

2.1 Cloning of the HuCAL VH3-Vk2 scFv fragment

In order to test the design of the consensus genes, one randomly chosen combination of synthetic light and heavy gene (HuCAL-Vκ2 and HuCAL-VH3) was used for the construction of a single-chain antibody (scFv) fragment. Briefly, the gene segments encoding the VH3 consensus gene and the CH1 gene segment including the CDR3 - framework 4 region, as well as the Vκ2 consensus gene and the Cκ gene segment including the CDR3 - framework 4 region were assembled yielding the gene for the VH3-CH1 Fd fragment and the gene encoding the Vκ2-Cκ light chain, respectively. The CH1 gene segment was then replaced by an oligonucleotide cassette encoding a 20-mer peptide linker with the sequence AGGGSGGGGSGGGGSGGGGS. The two oligonucleotides encoding this linker were 5'- TCAGCGGGTGGCGGTTCTGGCGGCGGTGGGAGCGGTGGCGGTGGTTC-TGGCGGTGGTGGTTCCGATATCGGTCCACGTACGG-3' and 5'-AATTCCGTACG-TGGACCGATATCGGAACCACCACCGCCAGAACCACCGCCACCGCTCCCACCGC CGCCAGAACCGCCACCCGC-3', respectively. Finally, the HuCAL-Vκ2 gene was inserted *via* EcoRV and BsiWI into the plasmid encoding the HuCAL-VH3-linker fusion, leading to the final gene HuCAL-VH3-Vκ2, which encoded the two consensus sequences in the single-chain format VH-linker-VL. The complete coding sequence is shown in Fig. 8.

2.2 Construction of a monovalent phage-display phagemid vector pIG10.3

Phagemid pIG10.3 (Fig. 9) was constructed in order to create a phage-display system (Winter et al., 1994) for the H3κ2 scFv gene. Briefly, the EcoRI/HindIII restriction fragment in the phagemid vector pIG10 (Ge et al., 1995) was replaced by the c-myc followed by an amber codon (which encodes an glutamate in the amber-suppresser strain XL1 Blue and a stop codon in the non-suppresser strain JM83) and a truncated version of the gene III (fusion junction at codon 249, see Lowman et al., 1991) through PCR mutagenesis.

2.3 Construction of H-CDR3 libraries

Heavy chain CDR3 libraries of two lengths (10 and 15 amino acids) were constructed using trinucleotide codon containing oligonucleotides (Virnekäs et al., 1994) as templates and the oligonucleotides complementing the flanking regions as primers. To concentrate only on the CDR3 structures that appear most often in functional antibodies, we kept the salt-bridge of R_{H94} and D_{H101} in the CDR3 loop. For the 15-mer library, both phenylalanine and methionine were introduced at position 100 since these two residues were found to occur quite often in human CDR3s of this length (not shown). For the same reason, valine and tyrosine were introduced at position 102. All other randomized positions contained codons for all amino acids except cystein, which was not used in the trinucleotide mixture.

The CDR3 libraries of lengths 10 and 15 were generated from the PCR fragments using oligonucleotide templates O3HCDR103T (5'- GATACGGCCGTGTATTA-TTGCGCGCGT $(TRI)_6$GATTATTGGGGCCAAGGCACCCTG-3') and O3HCDR153T (5'-GATACGGCCGT GTATTATTGCGCGCGT$(TRI)_{10}$(TTT/ATG)GAT(GTT/TAT)TGGG-GCCAAGGCACCCTG-3'), and primers O3HCDR35 (5'-GATACGGCCGTGTATTA-TTGC-3') and O3HCDR33 (5'-CAGGGTGCCTTGGCCCC-3'), where TRI are trinucleotide mixtures representing all amino acids without cystein, (TTT/ATG) and (GTT/TAT) are trinucleotide mixtures encoding the amino acids phenylalanine/methionine and valine/tyrosine, respectively. The potential diversity of these libraries was 4.7×10^7 and 3.4×10^{10} for 10-mer and 15-mer library, respectively. The library cassettes were first synthesized from PCR amplification of the oligo templates in the presence of both primers: 25 pmol of the oligo template O3HCDR103T or O3HCDR153T, 50 pmol each of the primers O3HCDR35 and O3HCDR33, 20 nmol of dNTP, 10x buffer and 2.5 units of Pfu DNA polymerase (Stratagene) in a total volume of 100 µl for 30 cycles (1 minute at 92°C, 1 minute at 62°C and 1 minute at 72°C). A hot-start procedure was used. The resulting mixtures were phenol-extracted, ethanol-precipitated and digested overnight with EagI and StyI. The vector pIG10.3-scH3κ2cat, where the EagI-StyI fragment in the vector pIG10.3-scH3κ2 encoding the H-CDR3 was replaced by the chloramphenicol acetyltransferase gene (cat) flanked with these two sites, was similarly digested. The digested vector (35 µg) was gel-purified and ligated with 100 µg of the library cassette overnight at 16°C. The ligation mixtures were isopropanol precipitated, air-dried and the pellets were redissolved in 100 µl of ddH2O. The ligation was mixed with 1 ml of freshly prepared electrocompetent XL1 Blue on ice. 20 rounds of electroporation were performed and the transformants were diluted in SOC medium, shaken at 37°C for 30 minutes and plated out on large LB plates (Amp/Tet/Glucose)

at 37°C for 6-9 hrs. The number of transformants (library size) was 3.2×10^7 and 2.3×10^7 for the 10-mer and the 15-mer library, respectively. The colonies were suspended in 2xYT medium (Amp/Tet/Glucose) and stored as glycerol culture.

In order to test the quality of the initial library, phagemids from 24 independent colonies (12 from the 10-mer and 12 from the 15-mer library, respectively) were isolated and analyzed by restriction digestion and sequencing. The restriction analysis of the 24 phagemids indicated the presence of intact vector in all cases. Sequence analysis of these clones (see Fig. 10) indicated that 22 out of 24 contained a functional sequence in their heavy chain CDR3 regions. 1 out of 12 clones of the 10-mer library had a CDR3 of length 9 instead of 10, and 2 out of 12 clones of the 15-mer library had no open reading frame, thereby leading to a non-functional scFv; one of these two clones contained two consecutive inserts, but out of frame (data not shown). All codons introduced were presented in an even distribution.

Expression levels of individual library members were also measured. Briefly, 9 clones from each library were grown in 2xYT medium containing Amp/Tet/0.5% glucose at 37°C overnight. Next day, the cultures were diluted into fresh medium with Amp/Tet. At an OD_{600nm} of 0.4, the cultures were induced with 1 mM of IPTG and shaken at RT overnight. Then the cell pellets were suspended in 1 ml of PBS buffer + 1 mM of EDTA. The suspensions were sonicated and the supernatants were separated on an SDS-PAGE under reducing conditions, blotted on nylon membrane and detected with anti-FLAG M1 antibody (see Fig. 11). From the nine clones of the 10-mer library, all express the scFv fragments. Moreover, the gene III / scFv fusion proteins were present in all cases. Among the nine clones from the 15-mer library analyzed, 6/9 (67%) led to the expression of both scFv and the gene III/scFv fusion proteins. More importantly, all clones expressing the scFvs and gene III/scFv fusions gave rise to about the same level of expression.

2.4 Biopanning

Phages displaying the antibody libraries were prepared using standard protocols. Phages derived from the 10-mer library were mixed with phages from the 15-mer library in a ratio of 20:1 (1×10^{10} cfu/well of the 10-mer and 5×10^8 cfu/well of the 15-mer phages, respectively). Subsequently, the phage solution was used for panning in ELISA plates (Maxisorp, Nunc) coated with FITC-BSA (Sigma) at concentration of 100 μg/ml in PBS at 4°C overnight. The antigen-coated wells were blocked with 3% powder milk in PBS and the phage solutions in 1% powder milk were added to each

well and the plate was shaken at RT for 1 hr. The wells were then washed with PBST and PBS (4 times each with shaking at RT for 5 minutes). The bound phages were eluted with 0.1 M triethylamine (TEA) at RT for 10 minutes. The eluted phage solutions were immediately neutralized with 1/2 the volume of 1 M Tris-Cl, pH 7.6. Eluted phage solutions (ca. 450 μl) were used to infect 5 ml of XL1 Blue cells at 37°C for 30 min. The infected cultures were then plated out on large LB plates (Amp/Tet/Glucose) and allowed to grow at 37°C until the colonies were visible. The colonies were suspended in 2xYT medium and the glycerol cultures were made as above described. This panning round was repeated twice, and in the third round elution was carried out with addition of fluorescein in a concentration of 100 μg/ml in PBS. The enrichment of specific phage antibodies was monitored by panning the initial as well as the subsequent fluorescein-specific sub-libraries against the blocking buffer (Fig. 12). Antibodies with specificity against fluorescein were isolated after 3 rounds of panning.

2.5 ELISA measurements

One of the criteria for the successful biopanning is the isolation of individual phage clones that bind to the targeted antigen or hapten. We undertook the isolation of anti-FITC phage antibody clones and characterized them first in a phage ELISA format. After the 3rd round of biopanning (see above), 24 phagemid containing clones were used to inoculate 100 μl of 2xYT medium (Amp/Tet/Glucose) in an ELISA plate (Nunc), which was subsequently shaken at 37°C for 5 hrs. 100 μl of 2xYT medium (Amp/Tet/1 mM IPTG) were added and shaking was continued for 30 minutes. A further 100 μl of 2xYT medium (Amp/Tet) containing the helper phage (1 x 10^9 cfu/well) was added and shaking was done at RT for 3 hrs. After addition of kanamycin to select for successful helper phage infection, the shaking was continued overnight. The plates were then centrifuged and the supernatants were pipetted directly into ELISA wells coated with 100 μl FITC-BSA (100μg/ml) and blocked with milk powder. Washing was performed similarly as during the panning procedure and the bound phages were detected with anti-M13 antibody-POD conjugate (Pharmacia) using soluble POD substrate (Boehringer-Mannheim). Of the 24 clones screened against FITC-BSA, 22 were active in the ELISA (Fig. 13). The initial libraries of similar titer gave rise to no detectable signal.
Specificity for fluorescein was measured in a competitive ELISA. Periplasmic fractions of five FITC specific scFvs were prepared as described above. Western blotting indicated that all clones expressed about the same amount of scFv fragment

(data not shown). ELISA was performed as described above, but additionally, the periplasmic fractions were incubated 30 min at RT either with buffer (no inhibition), with 10 mg/ml BSA (inhibition with BSA) or with 10 mg/ml fluorescein (inhibition with fluorescein) before adding to the well. Binding scFv fragment was detected using the anti-FLAG antibody M1. The ELISA signal could only be inhibited, when soluble fluorescein was added, indicating binding of the scFvs was specific for fluorescein (Fig. 14).

2.6 Sequence analysis

The heavy chain CDR3 region of 20 clones were sequenced in order to estimate the sequence diversity of fluorescein binding antibodies in the library (Fig. 15). In total, 16 of 20 sequences (80%) were different, showing that the constructed library contained a highly diverse repertoire of fluorescein binders. The CDR3s showed no particular sequence homology, but contained on average 4 arginine residues. This bias towards arginine in fluorescein binding antibodies had already been described by Barbas et al., 1992.

2.7 Production

E. coli JM83 was transformed with phagemid DNA of 3 selected clones and cultured in 0.5 L 2xYT medium. Induction was carried out with 1 mM IPTG at OD_{600nm} = 0.4 and growth was continued with vigorous shaking at RT overnight. The cells were harvested and pellets were suspended in PBS buffer and sonicated. The supernatants were separated from the cell debris via centrifugation and purified via the BioLogic system (Bio-Rad) by with a POROS®MC 20 column (IMAC, PerSeptive Biosystems, Inc.) coupled with an ion-exchange chromatography column. The ion-exchange column was one of the POROS®HS, CM or HQ or PI 20 (PerSeptive Biosystems, Inc.) depended on the theoretical pI of the scFv being purified. The pH of all the buffers was adjusted to one unit lower or higher than the pI of the scFv being purified throughout. The sample was loaded onto the first IMAC column, washed with 7 column volumes of 20 mM sodium phosphate, 1 M NaCl and 10 mM imidazole. This washing was followed by 7 column volumes of 20 mM sodium phosphate and 10 mM imidazole. Then 3 column volumes of an imidazole gradient (10 to 250 mM) were applied and the eluent was connected directly to the ion-exchanger. Nine column volumes of isocratic washing with 250 mM imidazole was followed by 15 column volumes of 250 mM to 100 mM and 7 column volumes of an imidazole / NaCl gradient (100 to 10 mM imidazole, 0 to 1 M NaCl). The flow rate was 5 ml/min. The purity of scFv fragments was checked by SDS-PAGE Coomassie

staining (Fig. 16). The concentration of the fragments was determined from the absorbance at 280 nm using the theoretically determined extinction coefficient (Gill & von Hippel, 1989). The scFv fragments could be purified to homogeneity (see Fig. 16). The yield of purified fragments ranged from 5 to 10 mg/L/OD.

Example 3: HuCAL H3κ2 Library Against a Collection of Antigens

In order to test the library used in Example 2 further, a new selection procedure was carried out using a variety of antigens comprising ß-estradiol, testosterone, Lewis-Y epitope (LeY), interleukin-2 (IL-2), lymphotoxin-ß (LT-ß), E-selectin ligand-1 (ESL-1), and BSA.

3.1 Biopanning

The library and all procedures were identical to those described in Example 2. The ELISA plates were coated with ß-estradiol-BSA (100 μg/ml), testosterone-BSA (100 μg/ml), LeY-BSA (20 μg/ml) IL-2 (20 μg/ml), ESL-1 (20 μg/ml) and BSA (100 μg/ml), LT-ß (denatured protein, 20 μg/ml). In the first two rounds, bound phages were eluted with 0.1 M triethylamine (TEA) at RT for 10 minutes. In the case of BSA, elution after three rounds of panning was carried out with addition of BSA in a concentration of 100 μg/ml in PBS. In the case of the other antigens, third round elution was done with 0.1 M triethylamine. In all cases except LeY, enrichment of binding phages could be seen (Figure 17). Moreover, a repetition of the biopanning experiment using only the 15-mer library resulted in the enrichment of LeY-binding phages as well (data not shown).

3.2. ELISA measurements

Clones binding to ß-estradiol, testosterone, LeY, LT-ß, ESL-1 and BSA were further analyzed and characterized as described in Example 2 for FITC. ELISA data for anti-ß-estradiol and anti-ESL-1 antibodies are shown in Fig. 18. In one experiment, selectivity and cross-reactivity of binding scFv fragments were tested. For this purpose, an ELISA plate was coated with FITC, testosterone, ß-estradiol, BSA, and ESL-1, with 5 wells for each antigen arranged in 5 rows, and 5 antibodies, one against each of the antigens, were screened against each of the antigens. Fig. 19

shows the specific binding of the antibodies to the antigen it was selected for, and the low cross-reactivity with the other four antigens.

3.3 Sequence analysis

The sequencing data of several clones against ß-estradiol (34 clones), testosterone (12 clones), LT-ß (23 clones), ESL-1 (34 clones), and BSA (10 clones) are given in Figures 20 to 24.

Example 4: Vector Construction

To be able to take advantage of the modularity of the consensus gene repertoire, a vector system had to be constructed which could be used in phage display screening of HuCAL libraries and subsequent optimization procedures. Therefore, all necessary vector elements such as origins of single-stranded or double-stranded replication, promotor/operator, repressor or terminator elements, resistance genes, potential recombination sites, gene III for display on filamentous phages, signal sequences, or detection tags had to be made compatible with the restriction site pattern of the modular consensus genes. Figure 25 shows a schematic representation of the pCAL vector system and the arrangement of vector modules and restriction sites therein. Figure 25a shows a list of all restriction sites which are already incorporated into the consensus genes or the vector elements as part of the modular system or which are not yet present in the whole system. The latter could be used in a later stage for the introduction of or within new modules.

4.1 Vector modules

A series of vector modules was constructed where the restriction sites flanking the gene sub-elements of the HuCAL genes were removed, the vector modules themselves being flanked by unique restriction sites. These modules were constructed either by gene synthesis or by mutagenesis of templates. Mutagenesis was done by add-on PCR, by site-directed mutagenesis (Kunkel et al., 1991) or multisite oligonucleotide-mediated mutagenesis (Sutherland et al., 1995; Perlak, 1990) using a PCR-based assembly method.

Figure 26 contains a list of the modules constructed. Instead of the terminator module M9 (HindIII-lpp-PacI), a larger cassette M9II was prepared to introduce FseI as additional restriction site. M9II can be cloned via HindIII/BsrGI.

All vector modules were characterized by restriction analysis and sequencing. In the case of module M11-II, sequencing of the module revealed a two-base difference in positions 164/65 compared to the sequence database of the template. These two different bases (CA → GC) created an additional BanII site. Since the same two-base difference occurs in the f1 origin of other bacteriophages, it can be assumed that the two-base difference was present in the template and not created by mutagenesis during cloning. This BanII site was removed by site-directed mutagenesis, leading to module M11-III. The BssSI site of module M14 could initially not be removed without impact on the function of the ColE1 origin, therefore M14-Ext2 was used for cloning of the first pCAL vector series. Figures 29 to 34 are showing the functional maps and sequences of the modules used for assembly of the modular vector pCAL4 (see below). The functional maps and sequences of additional modules can be found in Figure 35a. Figure 35b contains a list of oligonucleotides and primers used for the synthesis of the modules.

4.2 Cloning vector pMCS

To be able to assemble the individual vector modules, a cloning vector pMCS containing a specific multi-cloning site (MCS) was constructed. First, an MCS cassette (Fig. 27) was made by gene synthesis. This cassette contains all those restriction sites in the order necessary for the sequential introduction of all vector modules and can be cloned via the 5'-HindIII site and a four base overhang at the 3'-end compatible with an AatII site. The vector pMCS (Figure 28) was constructed by digesting pUC19 with AatII and HindIII, isolating the 2174 base pair fragment containing the bla gene and the ColE1 origin, and ligating the MCS cassette.

4.3 Cloning of modular vector pCAL4

This was cloned step by step by restriction digest of pMCS and subsequent ligation of the modules M1 (via AatII/XbaI), M7III (via EcoRI/HindIII), and M9II (via HindIII/BsrGI), and M11-II (via BsrGI/NheI). Finally, the bla gene was replaced by the cat gene module M17 (via AatII/BglII), and the wild type ColE1 origin by module M14-Ext2 (via BglII/NheI). Figure 35 is showing the functional map and the sequence of pCAL4.

4.4 Cloning of low-copy number plasmid vectors pCALO

A series of low-copy number plasmid vectors was constructed in a similar way using the p15A module M12 instead of the ColE1 module M14-Ext2. Figure 35a is showing the functional maps and sequences of the vectors pCALO1 to pCALO3.

Example 5: Construction of a HuCAL scFv Library

5.1. Cloning of all 49 HuCAL scFv fragments

All 49 combinations of the 7 HuCAL-VH and 7 HuCAL-VL consensus genes were assembled as described for the HuCAL VH3-Vκ2 scFv in Example 2 and inserted into the vector pBS12, a modified version of the pLisc series of antibody expression vectors (Skerra et *al.*, 1991).

5.2 Construction of a CDR cloning cassette

For replacement of CDRs, a universal ß-lactamase cloning cassette was constructed having a multi-cloning site at the 5'-end as well as at the 3'-end. The 5'-multi-cloning site comprises all restriction sites adjacent to the 5'-end of the HuCAL VH and VL CDRs, the 3'-multi-cloning site comprises all restriction sites adjacent to the 3' end of the HuCAL VH and VL CDRs. Both 5'- and 3'-multi-cloning site were prepared as cassettes via add-on PCR using synthetic oligonucleotides as 5'- and 3'-primers using wild type ß-lactamase gene as template. Figure 36 shows the functional map and the sequence of the cassette bla-MCS.

5.3. Preparation of VL-CDR3 library cassettes

The VL-CDR3 libraries comprising 7 random positions were generated from the PCR fragments using oligonucleotide templates Vκ1&Vκ3, Vκ2 and Vκ4 and primers O_K3L_5 and O_K3L_3 (Fig. 37) for the Vκ genes, and Vλ and primers O_L3L_5 (5'-GCAGAAGGCGAACGTCC-3') and O_L3LA_3 (Fig. 38) for the Vλ genes. Construction of the cassettes was performed as described in Example 2.3.

5.4 Cloning of HuCAL scFv genes with VL-CDR3 libraries

Each of the 49 single-chains was subcloned into pCAL4 via XbaI/EcoRI and the VL-CDR3 replaced by the ß-lactamase cloning cassette via BbsI/MscI, which was then replaced by the corresponding VL-CDR3 library cassette synthesized as described above. This CDR replacement is described in detail in Example 2.3 where the cat gene was used.

5.5 Preparation of VH-CDR3 library cassette

The VH-CDR3 libraries were designed and synthesized as described in Example 2.3.

5.6 Cloning of HuCAL scFv genes with VL- and VH-CDR3 libraries

Each of the 49 single-chain VL-CDR3 libraries was digested with BssHII/StyI to replace VH-CDR3. The "dummy" cassette digested with BssHII/StyI was inserted, and was then replaced by a corresponding VH-CDR3 library cassette synthesized as described above.

Example 6: Expression tests

Expression and toxicity studies were performed using the scFv format VH-linker-VL. All 49 combinations of the 7 HuCAL-VH and 7 HuCAL-VL consensus genes assembled as described in Example 5 were inserted into the vector pBS13, a modified version of the pLisc series of antibody expression vectors (Skerra et *al.*, 1991). A map of this vector is shown in Fig. 39.

E. coli JM83 was transformed 49 times with each of the vectors and stored as glycerol stock. Between 4 and 6 clones were tested simultaneously, always including the clone H3κ2, which was used as internal control throughout. As additional control, the McPC603 scFv fragment (Knappik & Plückthun, 1995) in pBS13 was expressed under identical conditions. Two days before the expression test was performed, the clones were cultivated on LB plates containing 30 μg/ml chloramphenicol and 60 mM glucose. Using this plates an 3 ml culture (LB medium

containing 90 μg chloramphenicol and 60 mM glucose) was inoculated overnight at 37 °C. Next day the overnight culture was used to inoculate 30 ml LB medium containing chloramphenicol (30 μg/ml). The starting OD_{600nm} was adjusted to 0.2 and a growth temperature of 30 °C was used. The physiology of the cells was monitored by measuring every 30 minutes for 8 to 9 hours the optical density at 600 nm. After the culture reached an OD_{600nm} of 0.5, antibody expression was induced by adding IPTG to a final concentration of 1 mM. A 5 ml aliquot of the culture was removed after 2 h of induction in order to analyze the antibody expression. The cells were lysed and the soluble and insoluble fractions of the crude extract were separated as described in Knappik & Plückthun, 1995. The fractions were assayed by reducing SDS-PAGE with the samples normalized to identical optical densities. After blotting and immunostaining using the α-FLAG antibody M1 as the first antibody (see Ge et *al.*, 1994) and an Fc-specific anti-mouse antiserum conjugated to alkaline phosphatase as the second antibody, the lanes were scanned and the intensities of the bands of the expected size (appr. 30 kDa) were quantified densitometrically and tabulated relative to the control antibody (see Fig. 40).

Example 7: Optimization of Fluorescein Binders

7.1. Construction of L-CDR3 and H-CDR2 library cassettes

A L-CDR3 library cassette was prepared from the oligonucleotide template CDR3L (5'-TGGAAGCTGAAGACGTGGGCGTGTATTATTGCCAGCAG(TR5)(TRI)$_4$CCG(TRI)-TTTGGCCAGGGTACGAAAGTT-3') and primer 5'-AACTTTCGTACCCTGGCC-3' for synthesis of the complementary strand, where (TRI) was a trinucleotide mixture representing all amino acids except Cys, (TR5) comprised a trinucleotide mixture representing the 5 codons for Ala, Arg, His, Ser, and Tyr.

A H-CDR2 library cassette was prepared from the oligonucleotide template CDRsH (5'-AGGGTCTCGAGTGGGTGAGC(TRI)ATT(TRI)$_{2\text{-}3}$(6)$_2$(TRI)ACC(TRI)TATGCGGATA-GCGTGAAAGGCCGTTTTACCATTTCACGTGATAATTCGAAAAACACCA-3'), and primer 5'-TGGTGTTTTTCGAATTATCA-3' for synthesis of the complementary strand, where (TRI) was a trinucleotide mixture representing all amino acids except Cys, (6) comprised the incorporation of (A/G) (A/C/G) T, resulting in the formation of 6 codons for Ala, Asn, Asp, Gly, Ser, and Thr, and the length distribution being obtained by performing one substoichiometric coupling of the (TRI) mixture during synthesis, omitting the capping step normally used in DNA synthesis.

DNA synthesis was performed on a 40 nmole scale, oligos were dissolved in TE buffer, purified via gel filtration using spin columns (S-200), and the DNA concentration determined by OD measurement at 260 nm (OD 1.0 = 40 μg/ml).

10 nmole of the oligonucleotide templates and 12 nmole of the corresponding primers were mixed and annealed at 80°C for 1 min, and slowly cooled down to 37°C within 20 to 30 min. The fill-in reaction was performed for 2 h at 37°C using Klenow polymerase (2.0 μl) and 250 nmole of each dNTP. The excess of dNTPs was removed by gel filtration using Nick-Spin columns (Pharmacia), and the double-stranded DNA digested with BbsI/MscI (L-CDR3), or XhoI/SfuI (H-CDR2) over night at 37°C. The cassettes were purified via Nick-Spin columns (Pharmacia), the concentration determined by OD measurement, and the cassettes aliquoted (15 pmole) for being stored at -80°C.

7.2 Library cloning:

DNA was prepared from the collection of FITC binding clones obtained in Example 2 (approx. 10^4 to clones). The collection of scFv fragments was isolated via XbaI/EcoRI digest. The vector pCAL4 (100 fmole, 10 μg) described in Example 4.3 was similarly digested with XbaI/EcoRI, gel-purified and ligated with 300 fmole of the scFv fragment collection over night at 16°C. The ligation mixture was isopropanol precipitated, air-dried, and the pellets were redissolved in 100 μl of dd H_2O. The ligation mixture was mixed with 1 ml of freshly prepared electrocompetent SCS 101 cells (for optimization of L-CDR3), or XL1 Blue cells (for optimization of H-CDR2) on ice. One round of electroporation was performed and the transformants were eluted in SOC medium, shaken at 37°C for 30 minutes, and an aliquot plated out on LB plates (Amp/Tet/Glucose) at 37°C for 6-9 hrs. The number of transformants was 5 x 10^4.

Vector DNA (100 μg) was isolated and digested (sequence and restriction map of scH3κ2 see Figure 8) with BbsI/MscI for optimization of L-CDR3, or XhoI/NspV for optimization of H-CDR2. 10 μg of purified vector fragments (5 pmole) were ligated with 15 pmole of the L-CDR3 or H-CDR2 library cassettes over night at 16°C. The ligation mixtures were isopropanol precipitated, air-dried, and the pellets were redissolved in 100 μl of dd H_2O. The ligation mixtures were mixed with 1 ml of freshly prepared electrocompetent XL1 Blue cells on ice. Electroporation was performed and the transformants were eluted in SOC medium and shaken at 37°C for 30 minutes. An aliquot was plated out on LB plates (Amp/Tet/Glucose) at 37°C for 6-9

hrs. The number of transformants (library size) was greater than 10^8 for both libraries. The libraries were stored as glycerol cultures.

7.3. Biopanning

This was performed as described for the initial H3κ2 H-CDR3 library in Example 2.1. Optimized scFvs binding to FITC could be characterized and analyzed as described in Example 2.2 and 2.3, and further rounds of optimization could be made if necessary.

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Table 1A: Human kappa germline gene segments

Used Name[1]	Reference[2]	Family[3]	Germline genes[4]
Vk1-1	9	1	O8; O18; DPK1
Vk1-2	1	1	L14; DPK2
Vk1-3	2	1	L15(1); HK101; HK146; HK189
Vk1-4	9	1	L11
Vk1-5	2	1	A30
Vk1-6	1	1	LFVK5
Vk1-7	1	1	LFVK431
Vk1-8	1	1	L1; HK137
Vk1-9	1	1	A20; DPK4
Vk1-10	1	1	L18; Va"
Vk1-11	1	1	L4; L18; Va'; V4a
Vk1-12	2	1	L5; L19(1); Vb; Vb4; DPK5; L19(2); Vb"; DPK6
Vk1-13	2	1	L15(2); HK134; HK166; DPK7
Vk1-14	8	1	L8; Vd; DPK8
Vk1-15	8	1	L9; Ve
Vk1-16	1	1	L12(1); HK102; V1
Vk1-17	2	1	L12(2)
Vk1-18	1	1	O12a (V3b)
Vk1-19	6	1	O2; O12; DPK9
Vk1-20	2	1	L24; Ve"; V13; DPK10
Vk1-21	1	1	O4; O14
Vk1-22	2	1	L22
Vk1-23	2	1	L23
Vk2-1	1	2	A2; DPK12
Vk2-2	6	2	O1; O11(1); DPK13
Vk2-3	6	2	O12(2); V3a
Vk2-4	2	2	L13
Vk2-5	1	2	DPK14
Vk2-6	4	2	A3; A19; DPK15
Vk2-7	4	2	A29; DPK27
Vk2-8	4	2	A13
Vk2-9	1	2	A23

Table 1A: (continued)

Used Name[1]	Reference[2]	Family[3]	Germline genes[4]
Vk2-10	4	2	A7; DPK17
Vk2-11	4	2	A17; DPK18
Vk2-12	4	2	A1; DPK19
Vk3-1	11	3	A11; humkv305; DPK20
Vk3-2	1	3	L20; Vg"
Vk3-3	2	3	L2; L16; humkv328; humkv328h2; humkv328h5; DPK21
Vk3-4	11	3	A27; humkv325; VkRF; DPK22
Vk3-5	2	3	L25; DPK23
Vk3-6	2	3	L10(1)
Vk3-7	7	3	L10(2)
Vk3-8	7	3	L6; Vg
Vk4-1	3	4	B3; VkIV; DPK24
Vk5-1	10	5	B2; EV15
Vk6-1	12	6	A14; DPK25
Vk6-2	12	6	A10; A26; DPK26
Vk7-1	5	7	B1

Table 1B: Human lambda germline gene segments

Used Name[1]	Reference[2]	Family[3]	Germline genes[4]
DPL1	1	1	
DPL2	1	1	HUMLV1L1
DPL3	1	1	HUMLV122
DPL4	1	1	VLAMBDA 1.1
HUMLV117	2	1	
DPL5	1	1	HUMLV117D
DPL6	1	1	
DPL7	1	1	IGLV1S2
DPL8	1	1	HUMLV1042
DPL9	1	1	HUMLV101
DPL10	1	2	
VLAMBDA 2.1	3	2	
DPL11	1	2	
DPL12	1	2	
DPL13	1	2	
DPL14	1	2	
DPL16	1	3	Humlv418; IGLV3S1
DPL23	1	3	VI III.1
Humlv318	4	3	
DPL18	1	7	4A; HUMIGLVA
DPL19	1	7	
DPL21	1	8	VL8.1
HUMLV801	5	8	
DPL22	1	9	
DPL24	1	unassigned	VLAMBDA N.2
gVLX-4.4	6	10	

Table 1C: Human heavy chain germline gene segments

Used Name[1]	Reference[2]	Family[3]	Germline genes[4]
VH1-12-1	19	1	DP10; DA-2; DA-6
VH1-12-8	22	1	RR.VH1:2
VH1-12-2	6	1	hv1263
VH1-12-9	7	1	YAC-7; RR.VH1.1; 1-69
VH1-12-3	19	1	DP3
VH1-12-4	19	1	DP21; 4d275a; VH7a
VH1-12-5	18	1	I-4.1b; V1-4.1b
VH1-12-6	21	1	1D37; VH7b ; 7-81; YAC-10
VH1-12-7	19	1	DP14; VH1GRR; V1-18
VH1-13-1	10	1	71-5; DP2
VH1-13-2	10	1	E3-10
VH1-13-3	19	1	DP1
VH1-13-4	12	1	V35
VH1-13-5	8	1	V1-2b
VH1-13-6	18	1	I-2; DP75
VH1-13-7	21	1	V1-2
VH1-13-8	19	1	DP8
VH1-13-9	3	1	1-1
VH1-13-10	19	1	DP12
VH1-13-11	15	1	V13C
VH1-13-12	18	1	I-3b; DP25; V1-3b
VH1-13-13	3	1	1-92
VH1-13-14	18	1	I-3; V1-3
VH1-13-15	19	1	DP15; V1-8
VH1-13-16	3	1	21-2; 3-1; DP7; V1-46
VH1-13-17	16	1	HG3
VH1-13-18	19	1	DP4; 7-2; V1-45
VH1-13-19	27	1	COS 5
VH1-1X-1	19	1	DP5; 1-24P
VH2-21-1	18	2	II-5b
VH2-31-1	2	2	VH2S12-1
VH2-31-2	2	2	VH2S12-7
VH2-31-3	2	2	VH2S12-9; DP27
VH2-31-4	2	2	VH2S12-10
VH2-31-5	14	2	V2-26; DP26; 2-26
VH2-31-6	15	2	VF2-26

Table 1C: (continued)

Used Name[1]	Reference[2]	Family[3]	Germline genes[4]
VH2-31-7	19	2	DP28; DA-7
VH2-31-14	7	2	YAC-3; 2-70
VH2-31-8	2	2	VH2S12-5
VH2-31-9	2	2	VH2S12-12
VH2-31-10	18	2	II-5; V2-5
VH2-31-11	2	2	VH2S12-2; VH2S12-8
VH2-31-12	2	2	VH2S12-4; VH2S12-6
VH2-31-13	2	2	VH2S12-14
VH3-11-1	13	3	v65-2; DP44
VH3-11-2	19	3	DP45
VH3-11-3	3	3	13-2; DP48
VH3-11-4	19	3	DP52
VH3-11-5	14	3	v3-13
VH3-11-6	19	3	DP42
VH3-11-7	3	3	8-1B; YAC-5; 3-66
VH3-11-8	14	3	V3-53
VH3-13-1	3	3	22-2B; DP35; V3-11
VH3-13-5	19	3	DP59; VH19; V3-35
VH3-13-6	25	3	f1-p1; DP61
VH3-13-7	19	3	DP46; GL-SJ2; COS 8; hv3005; hv3005f3; 3d21b; 56p1
VH3-13-8	24	3	VH26
VH3-13-9	5	3	vh26c
VH3-13-10	19	3	DP47; VH26; 3-23
VH3-13-11	3	3	1-91
VH3-13-12	19	3	DP58
VH3-13-13	3	3	1-9III; DP49; 3-30; 3d28.1
VH3-13-14	24	3	3019B9; DP50; 3-33; 3d277
VH3-13-15	27	3	COS 3
VH3-13-16	19	3	DP51
VH3-13-17	16	3	H11
VH3-13-18	19	3	DP53; COS 6; 3-74; DA-8
VH3-13-19	19	3	DP54; VH3-11; V3-7
VH3-13-20	14	3	V3-64; YAC-6
VH3-13-21	14	3	V3-48
VH3-13-22	14	3	V3-43; DP33
VH3-13-23	14	3	V3-33

Table 1C: (continued)

Used Name[1]	Reference[2]	Family[3]	Germline genes[4]
VH3-13-24	14	3	V3-21; DP77
VH3-13-25	14	3	V3-20; DP32
VH3-13-26	14	3	V3-9; DP31
VH3-14-1	3	3	12-2; DP29; 3-72; DA-3
VH3-14-4	7	3	YAC-9; 3-73; MTGL
VH3-14-2	4	3	VHD26
VH3-14-3	19	3	DP30
VH3-1X-1	1	3	LSG8.1; LSG9.1; LSG10.1; HUM12IGVH; HUM13IGVH
VH3-1X-2	1	3	LSG11.1; HUM4IGVH
VH3-1X-3	3	3	9-1; DP38; LSG7.1; RCG1.1; LSG1.1; LSG3.1; LSG5.1; HUM15IGVH; HUM2IGVH; HUM9IGVH
VH3-1X-4	1	3	LSG4.1
VH3-1X-5	1	3	LSG2.1
VH3-1X-6	1	3	LSG6.1; HUM10IGVH
VH3-1X-7	18	3	3-15; V3-15
VH3-1X-8	1	3	LSG12.1; HUM5IGVH
VH3-1X-9	14	3	V3-49
VH4-11-1	22	4	Tou-VH4.21
VH4-11-2	17	4	VH4.21; DP63; VH5; 4d76; V4-34
VH4-11-3	23	4	4.44
VH4-11-4	23	4	4.44.3
VH4-11-5	23	4	4.36
VH4-11-6	23	4	4.37
VH4-11-7	18	4	IV-4; 4.35; V4-4
VH4-11-8	17	4	VH4.11; 3d197d; DP71; 58p2
VH4-11-9	20	4	H7
VH4-11-10	20	4	H8
VH4-11-11	20	4	H9
VH4-11-12	17	4	VH4.16
VH4-11-13	23	4	4.38
VH4-11-14	17	4	VH4.15
VH4-11-15	11	4	58
VH4-11-16	10	4	71-4; V4-59
VH4-21-1	11	4	11
VH4-21-2	17	4	VH4.17; VH4.23; 4d255; 4.40; DP69
VH4-21-3	17	4	VH4.19; 79; V4-4b

Table 1C: (continued)

Used Name[1]	Reference[2]	Family[3]	Germline genes[4]
VH4-21-4	19	4	DP70; 4d68; 4.41
VH4-21-5	19	4	DP67; VH4-4B
VH4-21-6	17	4	VH4.22; VHSP; VH-JA
VH4-21-7	17	4	VH4.13; 1-9II; 12G-1; 3d28d; 4.42; DP68; 4-28
VH4-21-8	26	4	hv4005; 3d24d
VH4-21-9	17	4	VH4.14
VH4-31-1	23	4	4.34; 3d230d; DP78
VH4-31-2	23	4	4.34.2
VH4-31-3	19	4	DP64; 3d216d
VH4-31-4	19	4	DP65; 4-31; 3d277d
VH4-31-5	23	4	4.33; 3d75d
VH4-31-6	20	4	H10
VH4-31-7	20	4	H11
VH4-31-8	23	4	4.31
VH4-31-9	23	4	4.32
VH4-31-10	20	4	3d277d
VH4-31-11	20	4	3d216d
VH4-31-12	20	4	3d279d
VH4-31-13	17	4	VH4.18; 4d154; DP79
VH4-31-14	8	4	V4-39
VH4-31-15	11	4	2-1; DP79
VH4-31-16	23	4	4.30
VH4-31-17	17	4	VH4.12
VH4-31-18	10	4	71-2; DP66
VH4-31-19	23	4	4.39
VH4-31-20	8	4	V4-61
VH5-12-1	9	5	VH251; DP73; VHVCW; 51-R1; VHVLB; VHVCH; VHVTT; VHVAU; VHVBLK; VhAU; V5-51
VH5-12-2	17	5	VHVJB
VH5-12-3	3	5	1-v; DP80; 5-78
VH5-12-4	9	5	VH32; VHVRG; VHVMW; 5-2R1
VH6-35-1	4	6	VHVI; VH6; VHVIIS; VHVITE; VHVIJB; VHVICH; VHVICW; VHVIBLK; VHVIMW; DP74; 6-1G1; V6-1

Table 2A: rearranged human kappa sequences

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
III-3R	108	1	O8	1	1,1%	70
No.86	109	1	O8	3	3,2%	80
AU	108	1	O8	6	6,3%	103
ROY	108	1	O8	6	6,3%	43
IC4	108	1	O8	6	6,3%	70
HIV-B26	106	1	O8	3	3,2%	8
GRI	108	1	O8	8	8,4%	30
AG	106	1	O8	8	8,6%	116
REI	108	1	O8	9	9,5%	86
CLL PATIENT 16	88	1	O8	2	2,3%	122
CLL PATIENT 14	87	1	O8	2	2,3%	122
CLL PATIENT 15	88	1	O8	2	2,3%	122
GM4672	108	1	O8	11	11,6%	24
HUM. YFC51.1	108	1	O8	12	12,6%	110
LAY	108	1	O8	12	12,6%	48
HIV-b13	106	1	O8	9	9,7%	8
MAL-NaCl	108	1	O8	13	13,7%	102
STRAb SA-1A	108	1	O2	0	0,0%	120
HuVHCAMP	108	1	O8	13	13,7%	100
CRO	108	1	O2	10	10,5%	30
Am107	108	1	O2	12	12,6%	108
WALKER	107	1	O2	4	4,2%	57
III-2R	109	1	A20	0	0,0%	70
FOG1-A4	107	1	A20	4	4,2%	41
HK137	95	1	L1	0	0,0%	10
CEA4-8A	107	1	O2	7	7,4%	41
Va'	95	1	L4	0	0,0%	90
TR1.21	108	1	O2	4	4,2%	92
HAU	108	1	O2	6	6,3%	123
HK102	95	1	L12(1)	0	0,0%	9
H20C3K	108	1	L12(2)	3	3,2%	125
CHEB	108	1	O2	7	7,4%	5
HK134	95	1	L15(2)	0	0,0%	10
TEL9	108	1	O2	9	9,5%	73

Table 2A: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
TR1.32	103	1	O2	3	3,2%	92
RF-KES1	97	1	A20	4	4,2%	121
WES	108	1	L5	10	10,5%	61
DILp1	95	1	O4	1	1,1%	70
SA-4B	107	1	L12(2)	8	8,4%	120
HK101	95	1	L15(1)	0	0,0%	9
TR1.23	108	1	O2	5	5,3%	92
HF2-1/17	108	1	A30	0	0,0%	4
2E7	108	1	A30	1	1,1%	62
33.C9	107	1	L12(2)	7	7,4%	126
3D6	105	1	L12(2)	2	2,1%	34
I-2a	108	1	L8	8	8,4%	70
RF-KL1	97	1	L8	4	4,2%	121
TNF-E7	108	1	A30	9	9,5%	41
TR1.22	108	1	O2	7	7,4%	92
HIV-B35	106	1	O2	2	2,2%	8
HIV-b22	106	1	O2	2	2,2%	8
HIV-b27	106	1	O2	2	2,2%	8
HIV-B8	107	1	O2	10	10,8%	8
HIV-b8	107	1	O2	10	10,8%	8
RF-SJ5	95	1	A30	5	5,3%	113
GAL(I)	108	1	A30	6	6,3%	64
R3.5H5G	108	1	O2	6	6,3%	70
HIV-b14	106	1	A20	2	2,2%	8
TNF-E1	105	1	L5	8	8,4%	41
WEA	108	1	A30	8	8,4%	37
EU	108	1	L12(2)	5	5,3%	40
FOG1-G8	108	1	L8	11	11,6%	41
1X7RG1	108	1	L1	8	8,4%	70
BLI	108	1	L8	3	3,2%	72
KUE	108	1	L12(2)	11	11,6%	32
LUNm01	108	1	L12(2)	10	10,5%	6
HIV-b1	106	1	A20	4	4,3%	8
HIV-s4	103	1	O2	2	2,2%	8

Table 2A: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
CAR	107	1	L12(2)	11	11,7%	79
BR	107	1	L12(2)	11	11,6%	50
CLL PATIENT 10	88	1	O2	0	0,0%	122
CLL PATIENT 12	88	1	O2	0	0,0%	122
KING	108	1	L12(2)	12	12,6%	30
V13	95	1	L24	0	0,0%	46
CLL PATIENT 11	87	1	O2	0	0,0%	122
CLL PATIENT 13	87	1	O2	0	0,0%	122
CLL PATIENT 9	88	1	O12	1	1,1%	122
HIV-B2	106	1	A20	9	9,7%	8
HIV-b2	106	1	A20	9	9,7%	8
CLL PATIENT 5	88	1	A20	1	1,1%	122
CLL PATIENT 1	88	1	L8	2	2,3%	122
CLL PATIENT 2	88	1	L8	0	0,0%	122
CLL PATIENT 7	88	1	L5	0	0,0%	122
CLL PATIENT 8	88	1	L5	0	0,0%	122
HIV-b5	105	1	L5	11	12,0%	8
CLL PATIENT 3	87	1	L8	1	1,1%	122
CLL PATIENT 4	88	1	L9	0	0,0%	122
CLL PATIENT 18	85	1	L9	6	7,1%	122
CLL PATIENT 17	86	1	L12(2)	7	8,1%	122
HIV-b20	107	3	A27	11	11,7%	8
2C12	108	1	L12(2)	20	21,1%	68
1B11	108	1	L12(2)	20	21,1%	68
1H1	108	1	L12(2)	21	22,1%	68
2A12	108	1	L12(2)	21	22,1%	68
CUR	109	3	A27	0	0,0%	66
GLO	109	3	A27	0	0,0%	16
RF-TS1	96	3	A27	0	0,0%	121
GAR'	109	3	A27	0	0,0%	67
FLO	109	3	A27	0	0,0%	66
PIE	109	3	A27	0	0,0%	91
HAH 14.1	109	3	A27	1	1,0%	51
HAH 14.2	109	3	A27	1	1,0%	51

Table 2A: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
HAH 16.1	109	3	A27	1	1,0%	51
NOV	109	3	A27	1	1,0%	52
33.F12	108	3	A27	1	1,0%	126
8E10	110	3	A27	1	1,0%	25
TH3	109	3	A27	1	1,0%	25
HIC (R)	108	3	A27	0	0,0%	51
SON	110	3	A27	1	1,0%	67
PAY	109	3	A27	1	1,0%	66
GOT	109	3	A27	1	1,0%	67
mAbA6H4C5	109	3	A27	1	1,0%	12
BOR'	109	3	A27	2	2,1%	84
RF-SJ3	96	3	A27	2	2,1%	121
SIE	109	3	A27	2	2,1%	15
ESC	109	3	A27	2	2,1%	98
HEW'	110	3	A27	2	2,1%	98
YES8c	109	3	A27	3	3,1%	33
TI	109	3	A27	3	3,1%	114
mAb113	109	3	A27	3	3,1%	71
HEW	107	3	A27	0	0,0%	94
BRO	106	3	A27	0	0,0%	94
ROB	106	3	A27	0	0,0%	94
NG9	96	3	A27	4	4,2%	11
NEU	109	3	A27	4	4,2%	66
WOL	109	3	A27	4	4,2%	2
35G6	109	3	A27	4	4,2%	59
RF-SJ4	109	3	A11	0	0,0%	88
KAS	109	3	A27	4	4,2%	84
BRA	106	3	A27	1	1,1%	94
HAH	106	3	A27	1	1,1%	94
HIC	105	3	A27	0	0,0%	94
FS-2	109	3	A27	6	6,3%	87
JH'	107	3	A27	6	6,3%	38
EV1-15	109	3	A27	6	6,3%	83
SCA	108	3	A27	6	6,3%	65

Table 2A: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
mAb112	109	3	A27	6	6,3%	71
SIC	103	3	A27	3	3,3%	94
SA-4A	109	3	A27	6	6,3%	120
SER	108	3	A27	6	6,3%	98
GOL'	109	3	A27	7	7,3%	82
B5G10K	105	3	A27	9	9,7%	125
HG2B10K	110	3	A27	-9	9,4%	125
Taykv322	105	3	A27	5	5,4%	52
CLL PATIENT 24	89	3	A27	1	1,1%	122
HIV-b24	107	3	A27	7	7,4%	8
HIV-b6	107	3	A27	7	7,4%	8
Taykv310	99	3	A27	1	1,1%	52
KA3D1	108	3	L6	0	0,0%	85
19.E7	107	3	L6	0	0,0%	126
rsv6L	109	3	A27	12	12,5%	7
Taykv320	98	3	A27	1	1,2%	52
Vh	96	3	L10(2)	0	0,0%	89
LS8	108	3	L6	1	1,1%	109
LS1	108	3	L6	1	1,1%	109
LS2S3-3	107	3	L6	2	2,1%	99
LS2	108	3	L6	1	1,1%	109
LS7	108	3	L6	1	1,1%	109
LS2S3-4d	107	3	L6	2	2,1%	99
LS2S3-4a	107	3	L6	2	2,1%	99
LS4	108	3	L6	1	1,1%	109
LS6	108	3	L6	1	1,1%	109
LS2S3-10a	107	3	L6	2	2,1%	99
LS2S3-8c	107	3	L6	2	2,1%	99
LS5	108	3	L6	1	1,1%	109
LS2S3-5	107	3	L6	3	3,2%	99
LUNm03	109	3	A27	13	13,5%	6
IARC/BL41	108	3	A27	13	13,7%	55
slkv22	99	3	A27	3	3,5%	13
POP	108	3	L6	4	4,2%	111

Table 2A: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
LS2S3-10b	107	3	L6	3	3,2%	99
LS2S3-8f	107	3	L6	3	3,2%	99
LS2S3-12	107	3	L6	3	3,2%	99
HIV-B30	107	3	A27	11	11,7%	8
HIV-B20	107	3	A27	11	11,7%	8
HIV-b3	108	3	A27	11	11,7%	8
HIV-s6	104	3	A27	9	9,9%	8
YSE	107	3	L2/L16	1	1,1%	72
POM	109	3	L2/L16	9	9,4%	53
Humkv328	95	3	L2/L16	1	1,1%	19
CLL	109	3	L2/L16	3	3,2%	47
LES	96	3	L2/L16	3	3,2%	38
HIV-s5	104	3	A27	11	12,1%	8
HIV-s7	104	3	A27	11	12,1%	8
slkv1	99	3	A27	7	8,1%	13
Humka31es	95	3	L2/L16	4	4,2%	18
slkv12	101	3	A27	8	9,2%	13
RF-TS2	95	3	L2/L16	3	3,2%	121
II-1	109	3	L2/L16	4	4,2%	70
HIV-s3	105	3	A27	13	14,3%	8
RF-TMC1	96	3	L6	10	10,5%	121
GER	109	3	L2/L16	7	7,4%	75
GF4/1.1	109	3	L2/L16	8	8,4%	36
mAb114	109	3	L2/L16	6	6,3%	71
HIV-loop13	109	3	L2/L16	7	7,4%	8
bkv16	86	3	L6	1	1,2%	13
CLL PATIENT 29	86	3	L6	1	1,2%	122
slkv9	98	3	L6	3	3,5%	13
bkv17	99	3	L6	1	1,2%	13
slkv14	99	3	L6	1	1,2%	13
slkv16	101	3	L6	2	2,3%	13
bkv33	101	3	L6	4	4,7%	13
slkv15	99	3	L6	2	2,3%	13
bkv6	100	3	L6	3	3,5%	13

Table 2A: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
R6B8K	108	3	L2/L16	12	12,6%	125
AL 700	107	3	L2/L16	9	9,5%	117
slkv11	100	3	L2/L16	3	3,5%	13
slkv4	97	3	L6	4	4,8%	13
CLL PATIENT 26	87	3	L2/L16	1	1,1%	122
AL Se124	103	3	L2/L16	9	9,5%	117
slkv13	100	3	L2/L16	6	7,0%	13
bkv7	100	3	L2/L16	5	5,8%	13
bkv22	100	3	L2/L16	6	7,0%	13
CLL PATIENT 27	84	3	L2/L16	0	0,0%	122
bkv35	100	3	L6	8	9,3%	13
CLL PATIENT 25	87	3	L2/L16	4	4,6%	122
slkv3	86	3	L2/L16	7	8,1%	13
slkv7	99	1	O2	7	8,1%	13
HuFd79	111	3	L2/L16	24	24,2%	21
RAD	99	3	A27	9	10,3%	78
CLL PATIENT 28	83	3	L2/L16	4	4,8%	122
REE	104	3	L2/L16	25	27,2%	95
FR4	99	3	A27	8	9,2%	77
MD3.3	92	3	L6	1	1,3%	54
MD3.1	92	3	L6	0	0,0%	54
GA3.6	92	3	L6	2	2,6%	54
M3.5N	92	3	L6	3	3,8%	54
WEI'	82	3	A27	0	0,0%	65
MD3.4	92	3	L2/L16	1	1,3%	54
MD3.2	91	3	L6	3	3,8%	54
VER	97	3	A27	19	22,4%	20
CLL PATIENT 30	78	3	L6	3	3,8%	122
M3.1N	92	3	L2/L16	1	1,3%	54
MD3.6	91	3	L2/L16	0	0,0%	54
MD3.8	91	3	L2/L16	0	0,0%	54
GA3.4	92	3	L6	7	9,0%	54
M3.6N	92	3	A27	0	0,0%	54
MD3.10	92	3	A27	0	0,0%	54

Table 2A: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
MD3.13	91	3	A27	0	0,0%	54
MD3.7	93	3	A27	0	0,0%	54
MD3.9	93	3	A27	0	0,0%	54
GA3.1	93	3	A27	6	7,6%	54
bkv32	101	3	A27	5	5,7%	13
GA3.5	93	3	A27	5	6,3%	54
GA3.7	92	3	A27	7	8,9%	54
MD3.12	92	3	A27	2	2,5%	54
M3.2N	90	3	L6	6	7,8%	54
MD3.5	92	3	A27	1	1,3%	54
M3.4N	91	3	L2/L16	8	10,3%	54
M3.8N	91	3	L2/L16	7	9,0%	54
M3.7N	92	3	A27	3	3,8%	54
GA3.2	92	3	A27	9	11,4%	54
GA3.8	93	3	A27	4	5,1%	54
GA3.3	92	3	A27	8	10,1%	54
M3.3N	92	3	A27	5	6,3%	54
B6	83	3	A27	8	11,3%	78
E29.1 KAPPA	78	3	L2/L16	0	0,0%	22
SCW	108	1	O8	12	12,6%	31
REI-based CAMPATH-9	107	1	O8	14	14,7%	39
RZ	107	1	O8	14	14,7%	50
BI	108	1	O8	14	14,7%	14
AND	107	1	O2	13	13,7%	69
2A4	109	1	O2	12	12,6%	23
KA	108	1	O8	19	20,0%	107
MEV	109	1	O2	14	14,7%	29
DEE	106	1	O2	13	14,0%	76
OU(IOC)	108	1	O2	18	18,9%	60
HuRSV19VK	111	1	O8	21	21,0%	115
SP2	108	1	O2	17	17,9%	93
BJ26	99	1	O8	21	24,1%	1
NI	112	1	O8	24	24,2%	106
BMA 0310EUCIV2	106	1	L12(1)	21	22,3%	105

Table 2A: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
CLL PATIENT 6	71	1	A20	0	0,0%	122
BJ19	85	1	08	16	21,9%	1
GM 607	113	2	A3	0	0,0%	58
R5A3K	114	2	A3	1	1,0%	125
R1C8K	114	2	A3	1	1,0%	125
VK2.R149	113	2	A3	2	2,0%	118
TR1.6	109	2	A3	4	4,0%	92
TR1.37	104	2	A3	5	5,0%	92
FS-1	113	2	A3	6	6,0%	87
TR1.8	110	2	A3	6	6,0%	92
NIM	113	2	A3	8	8,0%	28
Inc	112	2	A3	11	11,0%	35
TEW	107	2	A3	6	6,4%	96
CUM	114	2	01	7	6,9%	44
HRF1	71	2	A3	4	5,6%	124
CLL PATIENT 19	87	2	A3	0	0,0%	122
CLL PATIENT 20	87	2	A3	0	0,0%	122
MIL	112	2	A3	16	16,2%	26
FR	113	2	A3	20	20,0%	101
MAL-Urine	83	1	02	6	8,6%	102
Taykv306	73	3	A27	1	1,6%	52
Taykv312	75	3	A27	1	1,6%	52
HIV-b29	93	3	A27	14	17,5%	8
1-185-37	110	3	A27	0	0,0%	119
1-187-29	110	3	A27	0	0,0%	119
TT117	110	3	A27	9	9,4%	63
HIV-loop8	108	3	A27	16	16,8%	8
rsv23L	108	3	A27	16	16,8%	7
HIV-b7	107	3	A27	14	14,9%	8
HIV-b11	107	3	A27	15	16,0%	8
HIV-LC1	107	3	A27	19	20,2%	8
HIV-LC7	107	3	A27	20	21,3%	8
HIV-LC22	107	3	A27	21	22,3%	8
HIV-LC13	107	3	A27	21	22,3%	8

Table 2A: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
HIV-LC3	107	3	A27	21	22,3%	8
HIV-LC5	107	3	A27	21	22,3%	8
HIV-LC28	107	3	A27	21	22,3%	8
HIV-b4	107	3	A27	22	23,4%	8
CLL PATIENT 31	87	3	A27	15	17,2%	122
HIV-loop2	108	3	L2/L16	17	17,9%	8
HIV-loop35	108	3	L2/L16	17	17,9%	8
HIV-LC11	107	3	A27	23	24,5%	8
HIV-LC24	107	3	A27	23	24,5%	8
HIV-b12	107	3	A27	24	25,5%	8
HIV-LC25	107	3	A27	24	25,5%	8
HIV-b21	107	3	A27	24	25,5%	8
HIV-LC26	107	3	A27	26	27,7%	8
G3D10K	108	1	L12(2)	12	12,6%	125
TT125	108	1	L5	8	8,4%	63
HIV-s2	103	3	A27	28	31,1%	8
265-695	108	1	L5	7	7,4%	3
2-115-19	108	1	A30	2	2,1%	119
rsv13L	107	1	O2	20	21,1%	7
HIV-b18	106	1	O2	14	15,1%	8
RF-KL5	98	3	L6	36	36,7%	97
ZM1-1	113	2	A17	7	7,0%	3
HIV-s8	103	1	O8	16	17,8%	8
K- EV15	95	5	B2	0	0,0%	112
RF-TS3	100	2	A23	0	0,0%	121
HF-21/28	111	2	A17	1	1,0%	17
RPMI6410	113	2	A17	1	1,0%	42
JC11	113	2	A17	1	1,0%	49
O-81	114	2	A17	5	5,0%	45
FK-001	113	4	B3	0	0,0%	81
CD5+.28	101	4	B3	1	1,0%	27
LEN	114	4	B3	1	1,0%	104
UC	114	4	B3	1	1,0%	111
CD5+.5	101	4	B3	1	1,0%	27

Table 2A: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
CD5+.26	101	4	B3	1	1,0%	27
CD5+.12	101	4	B3	2	2,0%	27
CD5+.23	101	4	B3	2	2,0%	27
CD5+.7	101	4	B3	2	2,0%	27
VJI	113	4	B3	3	3,0%	56
LOC	113	4	B3	3	3,0%	72
MAL	113	4	B3	3	3,0%	72
CD5+.6	101	4	B3	3	3,0%	27
H2F	113	4	B3	3	3,0%	70
PB17IV	114	4	B3	4	4,0%	74
CD5+.27	101	4	B3	4	4,0%	27
CD5+.9	101	4	B3	4	4,0%	27
CD5-.28	101	4	B3	5	5,0%	27
CD5-.26	101	4	B3	6	5,9%	27
CD5+.24	101	4	B3	6	5,9%	27
CD5+.10	101	4	B3	6	5,9%	27
CD5-.19	101	4	B3	6	5,9%	27
CD5-.18	101	4	B3	7	6,9%	27
CD5-.16	101	4	B3	8	7,9%	27
CD5-.24	101	4	B3	8	7,9%	27
CD5-.17	101	4	B3	10	9,9%	27
MD4.1	92	4	B3	0	0,0%	54
MD4.4	92	4	B3	0	0,0%	54
MD4.5	92	4	B3	0	0,0%	54
MD4.6	92	4	B3	0	0,0%	54
MD4.7	92	4	B3	0	0,0%	54
MD4.2	92	4	B3	1	1,3%	54
MD4.3	92	4	B3	5	6,3%	54
CLL PATIENT 22	87	2	A17	2	2,3%	122
CLL PATIENT 23	84	2	A17	2	2,4%	122

Table 2B: rearranged human lambda sequences

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
WAH	110	1	DPL3	7	7%	68
1B9/F2	112	1	DPL3	7	7%	9
DIA	112	1	DPL2	7	7%	36
mAb67	89	1	DPL3	0	0%	29
HiH2	110	1	DPL3	12	11%	3
NIG-77	112	1	DPL2	9	9%	72
OKA	112	1	DPL2	7	7%	84
KOL	112	1	DPL2	12	11%	40
T2:C5	111	1	DPL5	0	0%	6
T2:C14	110	1	DPL5	0	0%	6
PR-TS1	110	1	DPL5	0	0%	55
4G12	111	1	DPL5	1	1%	35
KIM46L	112	1	HUMLV117	0	0%	8
Fog-B	111	1	DPL5	3	3%	31
9F2L	111	1	DPL5	3	3%	79
mAb111	110	1	DPL5	3	3%	48
PHOX15	111	1	DPL5	4	4%	49
BL2	111	1	DPL5	4	4%	74
NIG-64	111	1	DPL5	4	4%	72
RF-SJ2	100	1	DPL5	6	6%	78
AL EZI	112	1	DPL5	7	7%	41
ZIM	112	1	HUMLV117	7	7%	18
RF-SJ1	100	1	DPL5	9	9%	78
IGLV1.1	98	1	DPL4	0	0%	1
NEW	112	1	HUMLV117	11	10%	42
CB-201	87	1	DPL2	1	1%	62
MEM	109	1	DPL2	6	6%	50
H210	111	2	DPL10	4	4%	45
NOV	110	2	DPL10	8	8%	25
NEI	111	2	DPL10	8	8%	24
AL MC	110	2	DPL11	6	6%	28
MES	112	2	DPL11	8	8%	84
FOG1-A3	111	2	DPL11	9	9%	27
AL NOV	112	2	DPL11	7	7%	28

Table 2B: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
HMST-1	110	2	DPL11	4	4%	82
HBW4-1	108	2	DPL12	9	9%	52
WH	110	2	DPL11	11	11%	34
11-50	110	2	DPL11	7	7%	82
HBp2	110	2	DPL12	8	8%	3
NIG-84	113	2	DPL11	12	11%	73
VIL	112	2	DPL11	9	9%	58
TRO	111	2	DPL12	10	10%	61
ES492	108	2	DPL11	15	15%	76
mAb216	89	2	DPL12	1	1%	7
BSA3	109	3	DPL16	0	0%	49
THY-29	110	3	DPL16	0	0%	27
PR-TS2	108	3	DPL16	0	0%	55
E29.1 LAMBDA	107	3	DPL16	1	1%	13
mAb63	109	3	DPL16	2	2%	29
TEL14	110	3	DPL16	6	6%	49
6H-3C4	108	3	DPL16	7	7%	39
SH	109	3	DPL16	7	7%	70
AL GIL	109	3	DPL16	8	8%	23
H6-3C4	108	3	DPL16	8	8%	83
V-lambda-2.DS	111	2	DPL11	3	3%	15
8.12 ID	110	2	DPL11	3	3%	81
DSC	111	2	DPL11	3	3%	56
PV11	110	2	DPL11	1	1%	56
33.H11	110	2	DPL11	4	4%	81
AS17	111	2	DPL11	7	7%	56
SD6	110	2	DPL11	7	7%	56
KS3	110	2	DPL11	9	9%	56
PV6	110	2	DPL12	5	5%	56
NGD9	110	2	DPL11	7	7%	56
MUC1-1	111	2	DPL11	11	10%	27
A30c	111	2	DPL10	6	6%	56
KS6	110	2	DPL12	6	6%	56
TEL13	111	2	DPL11	11	10%	49

Table 2B: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
AS7	110	2	DPL12	6	6%	56
MCG	112	2	DPL12	12	11%	20
U266L	110	2	DPL12	13	12%	77
PR-SJ2	110	2	DPL12	14	13%	55
BOH	112	2	DPL12	11	10%	37
TOG	111	2	DPL11	19	18%	53
TEL16	111	2	DPL11	19	18%	49
No.13	110	2	DPL10	14	13%	52
BO	112	2	DPL12	18	17%	80
WIN	112	2	DPL12	17	16%	11
BUR	104	2	DPL12	15	15%	46
NIG-58	110	2	DPL12	20	19%	69
WEIR	112	2	DPL11	26	25%	21
THY-32	111	1	DPL8	8	8%	27
TNF-H9G1	111	1	DPL8	9	9%	27
mAb61	111	1	DPL3	1	1%	29
LV1L1	98	1	DPL2	0	0%	54
HA	113	1	DPL3	14	13%	63
LA1L1	111	1	DPL2	3	3%	54
RHE	112	1	DPL1	17	16%	22
K1B12L	113	1	DPL8	17	16%	79
LOC	113	1	DPL2	15	14%	84
NIG-51	112	1	DPL2	12	11%	67
NEWM	104	1	DPL8	23	22%	10
MD3-4	106	3	DPL23	14	13%	4
COX	112	1	DPL2	13	12%	84
HiH10	106	3	DPL23	13	12%	3
VOR	112	1	DPL2	16	15%	16
AL POL	113	1	DPL2	16	15%	57
CD4-74	111	1	DPL2	19	18%	27
AMYLOID MOL	102	3	DPL23	15	15%	30
OST577	108	3	Humlv318	10	10%	4
NIG-48	113	1	DPL3	42	40%	66
CARR	108	3	DPL23	18	17%	19

Table 2B: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
mAb60	108	3	DPL23	14	13%	29
NIG-68	99	3	DPL23	25	26%	32
KERN	107	3	DPL23	26	25%	59
ANT	106	3	DPL23	17	16%	19
LEE	110	3	DPL23	18	17%	85
CLE	94	3	DPL23	17	17%	19
VL8	98	8	DPL21	0	0%	81
MOT	110	3	Humlv318	23	22%	38
GAR	108	3	DPL23	26	25%	33
32.B9	98	8	DPL21	5	5%	81
PUG	108	3	Humlv318	24	23%	19
T1	115	8	HUMLV801	52	50%	6
RF-TS7	96	7	DPL18	4	4%	60
YM-1	116	8	HUMLV801	51	49%	75
K6H6	112	8	HUMLV801	20	19%	44
K5C7	112	8	HUMLV801	20	19%	44
K5B8	112	8	HUMLV801	20	19%	44
K5G5	112	8	HUMLV801	20	19%	44
K4B8	112	8	HUMLV801	19	18%	44
K6F5	112	8	HUMLV801	17	16%	44
HIL	108	3	DPL23	22	21%	47
KIR	109	3	DPL23	20	19%	19
CAP	109	3	DPL23	19	18%	84
1B8	110	3	DPL23	22	21%	43
SHO	108	3	DPL23	19	18%	19
HAN	108	3	DPL23	20	19%	19
cML23	96	3	DPL23	3	3%	12
PR-SJ1	96	3	DPL23	7	7%	55
BAU	107	3	DPL23	9	9%	5
TEX	99	3	DPL23	8	8%	19
X(PET)	107	3	DPL23	9	9%	51
DOY	106	3	DPL23	9	9%	19
COT	106	3	DPL23	13	12%	19
Pag-1	111	3	Humlv318	5	5%	31

Table 2B: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
DIS	107	3	Humlv318	2	2%	19
WIT	108	3	Humlv318	7	7%	19
I.RH	108	3	Humlv318	12	11%	19
S1-1	108	3	Humlv318	12	11%	52
DEL	108	3	Humlv318	14	13%	17
TYR	108	3	Humlv318	11	10%	19
J.RH	109	3	Humlv318	13	12%	19
THO	112	2	DPL13	38	36%	26
LBV	113	1	DPL3	38	36%	2
WLT	112	1	DPL3	33	31%	14
SUT	112	2	DPL12	37	35%	65

Table 2C: rearranged human heavy chain sequences

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
21/28	119	1	VH1-13-12	0	0,0%	31
8E10	123	1	VH1-13-12	0	0,0%	31
MUC1-1	118	1	VH1-13-6	4	4,1%	42
gF1	98	1	VH1-13-12	10	10,2%	75
VHGL 1.2	98	1	VH1-13-6	2	2,0%	26
HV1L1	98	1	VH1-13-6	0	0,0%	81
RF-TS7	104	1	VH1-13-6	3	3,1%	96
E55 1.A15	106	1	VH1-13-15	1	1,0%	26
HA1L1	126	1	VH1-13-6	7	7,1%	81
UC	123	1	VH1-13-6	5	5,1%	115
WIL2	123	1	VH1-13-6	6	6,1%	55
R3.5H5G	122	1	VH1-13-6	10	10,2%	70
N89P2	123	1	VH1-13-16	11	11,2%	77
mAb113	126	1	VH1-13-6	10	10,2%	71
LS2S3-3	125	1	VH1-12-7	5	5,1%	98
LS2S3-12a	125	1	VH1-12-7	5	5,1%	98
LS2S3-5	125	1	VH1-12-7	5	5,1%	98
LS2S3-12e	125	1	VH1-12-7	5	5,1%	98
LS2S3-4	125	1	VH1-12-7	5	5,1%	98
LS2S3-10	125	1	VH1-12-7	5	5,1%	98
LS2S3-12d	125	1	VH1-12-7	6	6,1%	98
LS2S3-8	125	1	VH1-12-7	5	5,1%	98
LS2	125	1	VH1-12-7	6	6,1%	113
LS4	105	1	VH1-12-7	6	6,1%	113
LS5	125	1	VH1-12-7	6	6,1%	113
LS1	125	1	VH1-12-7	6	6,1%	113
LS6	125	1	VH1-12-7	6	6,1%	113
LS8	125	1	VH1-12-7	7	7,1%	113
THY-29	122	1	VH1-12-7	0	0,0%	42
1B9/F2	122	1	VH1-12-7	10	10,2%	21
51P1	122	1	VH1-12-1	0	0,0%	105
NEI	127	1	VH1-12-1	0	0,0%	55
AND	127	1	VH1-12-1	0	0,0%	55
L7	127	1	VH1-12-1	0	0,0%	54
L22	124	1	VH1-12-1	0	0,0%	54
L24	127	1	VH1-12-1	0	0,0%	54

Table 2C: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
L26	116	1	VH1-12-1	0	0,0%	54
L33	119	1	VH1-12-1	0	0,0%	54
L34	117	1	VH1-12-1	0	0,0%	54
L36	118	1	VH1-12-1	0	0,0%	54
L39	120	1	VH1-12-1	0	0,0%	54
L41	120	1	VH1-12-1	0	0,0%	54
L42	125	1	VH1-12-1	0	0,0%	54
VHGL 1.8	101	1	VH1-12-1	0	0,0%	26
783c	127	1	VH1-12-1	0	0,0%	22
X17115	127	1	VH1-12-1	0	0,0%	37
L25	124	1	VH1-12-1	0	0,0%	54
L17	120	1	VH1-12-1	1	1,0%	54
L30	127	1	VH1-12-1	1	1,0%	54
L37	120	1	VH1-12-1	1	1,0%	54
TNF-E7	116	1	VH1-12-1	2	2,0%	42
mAb111	122	1	VH1-12-1	7	7,1%	71
III-2R	122	1	VH1-12-9	3	3,1%	70
KAS	121	1	VH1-12-1	7	7,1%	79
YES8c	122	1	VH1-12-1	8	8,2%	34
RF-TS1	123	1	VH1-12-1	8	8,2%	82
BOR'	121	1	VH1-12-8	7	7,1%	79
VHGL 1.9	101	1	VH1-12-1	8	8,2%	26
mAb410.30F305	117	1	VH1-12-9	5	5,1%	52
EV1-15	127	1	VH1-12-8	10	10,2%	78
mAb112	122	1	VH1-12-1	11	11,2%	71
EU	117	1	VH1-12-1	11	11,2%	28
H210	127	1	VH1-12-1	12	12,2%	66
TRANSGENE	104	1	VH1-12-1	0	0,0%	111
CLL2-1	93	1	VH1-12-1	0	0,0%	30
CLL10 13-3	97	1	VH1-12-1	0	0,0%	29
LS7	99	1	VH1-12-7	4	4,1%	113
ALL7-1	87	1	VH1-12-7	0	0,0%	30
CLL3-1	91	1	VH1-12-7	1	1,0%	30
ALL56-1	85	1	VH1-13-8	0	0,0%	30
ALL1-1	87	1	VH1-13-6	1	1,0%	30
ALL4-1	94	1	VH1-13-8	0	0,0%	30

Table 2C: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
ALL56 15-4	85	1	VH1-13-8	5	5,1%	29
CLL4-1	88	1	VH1-13-1	1	1,0%	30
Au92.1	98	1	VH1-12-5	0	0,0%	49
RF-TS3	120	1	VH1-12-5	1	1,0%	82
Au4.1	98	1	VH1-12-5	1	1,0%	49
HP1	121	1	VH1-13-6	13	13,3%	110
BLI	127	1	VH1-13-15	5	5,1%	72
No.13	127	1	VH1-12-2	19	19,4%	76
TR1.23	122	1	VH1-13-2	23	23,5%	88
S1-1	125	1	VH1-12-2	18	18,4%	76
TR1.10	119	1	VH1-13-12	14	14,3%	88
E55 1.A2	102	1	VH1-13-15	3	3,1%	26
SP2	119	1	VH1-13-6	15	15,3%	89
TNF-H9G1	111	1	VH1-13-18	2	2,0%	42
G3D10H	127	1	VH1-13-16	19	19,4%	127
TR1.9	118	1	VH1-13-12	14	14,3%	88
TR1.8	121	1	VH1-12-1	24	24,5%	88
LUNm01	127	1	VH1-13-6	22	22,4%	9
K1B12H	127	1	VH1-12-7	23	23,5%	127
L3B2	99	1	VH1-13-6	2	2,0%	46
ss2	100	1	VH1-13-6	2	2,0%	46
No.86	124	1	VH1-12-1	20	20,4%	76
TR1.6	124	1	VH1-12-1	19	19,4%	88
ss7	99	1	VH1-12-7	3	3,1%	46
s5B7	102	1	VH1-12-1	0	0,0%	46
s6A3	97	1	VH1-12-1	0	0,0%	46
ss6	99	1	VH1-12-1	0	0,0%	46
L2H7	103	1	VH1-13-12	0	0,0%	46
s6BG8	93	1	VH1-13-12	0	0,0%	46
s6C9	107	1	VH1-13-12	0	0,0%	46
HIV-b4	124	1	VH1-13-12	21	21,4%	12
HIV-b12	124	1	VH1-13-12	21	21,4%	12
L3G5	98	1	VH1-13-6	1	1,0%	46
22	115	1	VH1-13-6	11	11,2%	118
L2A12	99	1	VH1-13-15	3	3,1%	46
PHOX15	124	1	VH1-12-7	20	20,4%	73

Table 2C: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
LUNm03	127	1	VH1-1X-1	18	18,4%	9
CEA4-8A	129	1	VH1-12-7	1	1,0%	42
M60	121	2	VH2-31-3	3	3,0%	103
HiH10	127	2	VH2-31-5	9	9,0%	4
COR	119	2	VH2-31-2	11	11,0%	91
2-115-19	124	2	VH2-31-11	8	8,1%	124
OU	125	2	VH2-31-14	20	25,6%	92
HE	120	2	VH2-31-13	19	19,0%	27
CLL33 40-1	78	2	VH2-31-5	2	2,0%	29
E55 3.9	88	3	VH3-11-5	7	7,2%	26
MTFC3	125	3	VH3-14-4	21	21,0%	131
MTFC11	125	3	VH3-14-4	21	21,0%	131
MTFJ1	114	3	VH3-14-4	21	21,0%	131
MTFJ2	114	3	VH3-14-4	21	21,0%	131
MTFUJ4	100	3	VH3-14-4	21	21,0%	131
MTFUJ5	100	3	VH3-14-4	21	21,0%	131
MTFUJ2	100	3	VH3-14-4	22	22,0%	131
MTFC8	125	3	VH3-14-4	23	23,0%	131
TD e Vq	113	3	VH3-14-4	0	0,0%	16
rMTF	114	3	VH3-14-4	5	5,0%	131
MTFUJ6	100	3	VH3-14-4	10	10,0%	131
RF-KES	107	3	VH3-14-4	9	9,0%	85
N51P8	126	3	VH3-14-1	9	9,0%	77
TEI	119	3	VH3-13-8	21	21,4%	20
33.H11	115	3	VH3-13-19	10	10,2%	129
SB1/D8	101	3	VH3-1X-8	14	14,0%	2
38P1	119	3	VH3-11-3	0	0,0%	104
BRO'IGM	119	3	VH3-11-3	13	13,4%	19
NIE	119	3	VH3-13-7	15	15,3%	87
3D6	126	3	VH3-13-26	5	5,1%	35
ZM1-1	112	3	VH3-11-3	8	8,2%	5
E55 3.15	110	3	VH3-13-26	0	0,0%	26
gF9	108	3	VH3-13-8	15	15,3%	75
THY-32	120	3	VH3-13-26	3	3,1%	42
RF-KL5	100	3	VH3-13-26	5	5,1%	96
OST577	122	3	VH3-13-13	6	6,1%	5

Table 2C: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
BO	113	3	VH3-13-19	15	15,3%	10
TT125	121	3	VH3-13-10	15	15,3%	64
2-115-58	127	3	VH3-13-10	11	11,2%	124
KOL	126	3	VH3-13-14	16	16,3%	102
mAb60	118	3	VH3-13-17	14	14,3%	45
RF-AN	106	3	VH3-13-26	8	8,2%	85
BUT	115	3	VH3-11-6	13	13,4%	119
KOL-based CAMPATH-9	118	3	VH3-13-13	16	16,3%	41
B1	119	3	VH3-13-19	13	13,3%	53
N98P1	127	3	VH3-13-1	13	13,3%	77
TT117	107	3	VH3-13-10	12	12,2%	64
WEA	114	3	VH3-13-12	15	15,3%	40
HIL	120	3	VH3-13-14	14	14,3%	23
s5A10	97	3	VH3-13-14	0	0,0%	46
s5D11	98	3	VH3-13-7	0	0,0%	46
s6C8	100	3	VH3-13-7	0	0,0%	46
s6H12	98	3	VH3-13-7	0	0,0%	46
VH10.7	119	3	VH3-13-14	16	16,3%	128
HIV-loop2	126	3	VH3-13-7	16	16,3%	12
HIV-loop35	126	3	VH3-13-7	16	16,3%	12
TRO	122	3	VH3-13-1	13	13,3%	61
SA-4B	123	3	VH3-13-1	15	15,3%	125
L2B5	98	3	VH3-13-13	0	0,0%	46
s6E11	95	3	VH3-13-13	0	0,0%	46
s6H7	100	3	VH3-13-13	0	0,0%	46
ss1	102	3	VH3-13-13	0	0,0%	46
ss8	94	3	VH3-13-13	0	0,0%	46
DOB	120	3	VH3-13-26	21	21,4%	116
THY-33	115	3	VH3-13-15	20	20,4%	42
NOV	118	3	VH3-13-19	14	14,3%	38
rsv13H	120	3	VH3-13-24	20	20,4%	11
L3G11	98	3	VH3-13-20	2	2,0%	46
L2E8	99	3	VH3-13-19	0	0,0%	46
L2D10	101	3	VH3-13-10	1	1,0%	46
L2E7	98	3	VH3-13-10	1	1,0%	46

Table 2C: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
L3A10	100	3	VH3-13-24	0	0,0%	46
L2E5	97	3	VH3-13-2	1	1,0%	46
BUR	119	3	VH3-13-7	21	21,4%	67
s4D5	107	3	VH3-11-3	1	1,0%	46
19	116	3	VH3-13-16	4	4,1%	118
s5D4	99	3	VH3-13-1	0	0,0%	46
s6A8	100	3	VH3-13-1	0	0,0%	46
HIV-loop13	123	3	VH3-13-12	17	17,3%	12
TR1.32	112	3	VH3-11-8	18	18,6%	88
L2B10	97	3	VH3-11-3	1	1,0%	46
TR1.5	114	3	VH3-11-8	21	21,6%	88
s6H9	101	3	VH3-13-25	0	0,0%	46
8	112	3	VH3-13-1	6	6,1%	118
23	115	3	VH3-13-1	6	6,1%	118
7	115	3	VH3-13-1	4	4,1%	118
TR1.3	120	3	VH3-11-8	20	20,6%	88
18/2	125	3	VH3-13-10	0	0,0%	32
18/9	125	3	VH3-13-10	0	0,0%	31
30P1	119	3	VH3-13-10	0	0,0%	106
HF2-1/17	125	3	VH3-13-10	0	0,0%	8
A77	109	3	VH3-13-10	0	0,0%	44
B19.7	108	3	VH3-13-10	0	0,0%	44
M43	119	3	VH3-13-10	0	0,0%	103
1/17	125	3	VH3-13-10	0	0,0%	31
18/17	125	3	VH3-13-10	0	0,0%	31
E54 3.4	109	3	VH3-13-10	0	0,0%	26
LAMBDA-VH26	98	3	VH3-13-10	1	1,0%	95
E54 3.8	111	3	VH3-13-10	1	1,0%	26
GL16	106	3	VH3-13-10	1	1,0%	44
4G12	125	3	VH3-13-10	1	1,0%	56
A73	106	3	VH3-13-10	2	2,0%	44
AL1.3	111	3	VH3-13-10	3	3,1%	117
3.A290	118	3	VH3-13-10	2	2,0%	108
Ab18	127	3	VH3-13-8	2	2,0%	100
E54 3.3	105	3	VH3-13-10	3	3,1%	26
35G6	121	3	VH3-13-10	3	3,1%	57

Table 2C: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
A95	107	3	VH3-13-10	5	5,1%	44
Ab25	128	3	VH3-13-10	5	5,1%	100
N87	126	3	VH3-13-10	4	4,1%	77
ED8.4	99	3	VH3-13-10	6	6,1%	2
RF-KL1	122	3	VH3-13-10	6	6,1%	82
AL1.1	112	3	VH3-13-10	2	2,0%	117
AL3.11	102	3	VH3-13-10	1	1,0%	117
32.B9	127	3	VH3-13-8	6	6,1%	129
TK1	109	3	VH3-13-10	2	2,0%	117
POP	123	3	VH3-13-10	8	8,2%	115
9F2H	127	3	VH3-13-10	9	9,2%	127
VD	115	3	VH3-13-10	9	9,2%	10
Vh38Cl.10	121	3	VH3-13-10	8	8,2%	74
Vh38Cl.9	121	3	VH3-13-10	8	8,2%	74
Vh38Cl.8	121	3	VH3-13-10	8	8,2%	74
63P1	120	3	VH3-11-8	0	0,0%	104
60P2	117	3	VH3-11-8	0	0,0%	104
AL3.5	90	3	VH3-13-10	2	2,0%	117
GF4/1.1	123	3	VH3-13-10	10	10,2%	39
Ab21	126	3	VH3-13-10	12	12,2%	100
TD d Vp	118	3	VH3-13-17	2	2,0%	16
Vh38Cl.4	119	3	VH3-13-10	8	8,2%	74
Vh38Cl.5	119	3	VH3-13-10	8	8,2%	74
AL3.4	104	3	VH3-13-10	1	1,0%	117
FOG1-A3	115	3	VH3-13-19	2	2,0%	42
HA3D1	117	3	VH3-13-21	1	1,0%	81
E54 3.2	112	3	VH3-13-24	0	0,0%	26
mAb52	128	3	VH3-13-12	2	2,0%	51
mAb53	128	3	VH3-13-12	2	2,0%	51
mAb56	128	3	VH3-13-12	2	2,0%	51
mAb57	128	3	VH3-13-12	2	2,0%	51
mAb58	128	3	VH3-13-12	2	2,0%	51
mAb59	128	3	VH3-13-12	2	2,0%	51
mAb105	128	3	VH3-13-12	2	2,0%	51
mAb107	128	3	VH3-13-12	2	2,0%	51
E55 3.14	110	3	VH3-13-19	0	0,0%	26

Table 2C: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
F13-28	106	3	VH3-13-19	1	1,0%	94
mAb55	127	3	VH3-13-18	4	4,1%	51
YSE	117	3	VH3-13-24	6	6,1%	72
E55 3.23	106	3	VH3-13-19	2	2,0%	26
RF-TS5	101	3	VH3-13-1	3	3,1%	85
N42P5	124	3	VH3-13-2	7	7,1%	77
FOG1-H6	110	3	VH3-13-16	7	7,1%	42
0-81	115	3	VH3-13-19	11	11,2%	47
HIV-s8	122	3	VH3-13-12	11	11,2%	12
mAb114	125	3	VH3-13-19	12	12,2%	71
33.F12	116	3	VH3-13-2	4	4,1%	129
4B4	119	3	VH3-1X-3	0	0,0%	101
M26	123	3	VH3-1X-3	0	0,0%	103
VHGL 3.1	100	3	VH3-1X-3	0	0,0%	26
E55 3.13	113	3	VH3-1X-3	1	1,0%	26
SB5/D6	101	3	VH3-1X-6	3	3,0%	2
RAY4	101	3	VH3-1X-6	3	3,0%	2
82-D V-D	106	3	VH3-1X-3	5	5,0%	112
MAL	129	3	VH3-1X-3	5	5,0%	72
LOC	123	3	VH3-1X-6	5	5,0%	72
LSF2	101	3	VH3-1X-6	11	11,0%	2
HIB RC3	100	3	VH3-1X-6	11	11,0%	1
56P1	119	3	VH3-13-7	0	0,0%	104
M72	122	3	VH3-13-7	0	0,0%	103
M74	121	3	VH3-13-7	0	0,0%	103
E54 3.5	105	3	VH3-13-7	0	0,0%	26
2E7	123	3	VH3-13-7	0	0,0%	63
2P1	117	3	VH3-13-7	0	0,0%	104
RF-SJ2	127	3	VH3-13-7	1	1,0%	83
PR-TS1	114	3	VH3-13-7	1	1,0%	85
KIM46H	127	3	VH3-13-13	0	0,0%	18
E55 3.6	108	3	VH3-13-7	2	2,0%	26
E55 3.10	107	3	VH3-13-13	1	1,0%	26
3.B6	114	3	VH3-13-13	1	1,0%	108
E54 3.6	110	3	VH3-13-13	1	1,0%	26
FL2-2	114	3	VH3-13-13	1	1,0%	80

Table 2C: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
RF-SJ3	112	3	VH3-13-7	2	2,0%	85
E55 3.5	105	3	VH3-13-14	1	1,0%	26
BSA3	121	3	VH3-13-13	1	1,0%	73
HMST-1	119	3	VH3-13-7	3	3,1%	130
RF-TS2	126	3	VH3-13-13	4	4,1%	82
E55 3.12	109	3	VH3-13-15	0	0,0%	26
19.E7	126	3	VH3-13-14	3	3,1%	129
11-50	119	3	VH3-13-13	6	6,1%	130
E29.1	120	3	VH3-13-15	2	2,0%	25
E55 3.16	108	3	VH3-13-7	6	6,1%	26
TNF-E1	117	3	VH3-13-7	7	7,1%	42
RF-SJ1	127	3	VH3-13-13	6	6,1%	83
FOG1-A4	116	3	VH3-13-7	8	8,2%	42
TNF-A1	117	3	VH3-13-15	4	4,1%	42
PR-SJ2	107	3	VH3-13-14	8	8,2%	85
HN.14	124	3	VH3-13-13	10	10,2%	33
CAM'	121	3	VH3-13-7	12	12,2%	65
HIV-B8	125	3	VH3-13-7	9	9,2%	12
HIV-b27	125	3	VH3-13-7	9	9,2%	12
HIV-b8	125	3	VH3-13-7	9	9,2%	12
HIV-s4	125	3	VH3-13-7	9	9,2%	12
HIV-B26	125	3	VH3-13-7	9	9,2%	12
HIV-B35	125	3	VH3-13-7	10	10,2%	12
HIV-b18	125	3	VH3-13-7	10	10,2%	12
HIV-b22	125	3	VH3-13-7	11	11,2%	12
HIV-b13	125	3	VH3-13-7	12	12,2%	12
333	117	3	VH3-14-4	24	24,0%	24
1H1	120	3	VH3-14-4	24	24,0%	24
1B11	120	3	VH3-14-4	23	23,0%	24
CLL30 2-3	86	3	VH3-13-19	1	1,0%	29
GA	110	3	VH3-13-7	19	19,4%	36
JeB	99	3	VH3-13-14	3	3,1%	7
GAL	110	3	VH3-13-19	10	10,2%	126
K6H6	119	3	VH3-1X-6	18	18,0%	60
K4B8	119	3	VH3-1X-6	18	18,0%	60
K5B8	119	3	VH3-1X-6	18	18,0%	60

Table 2C: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
K5C7	119	3	VH3-1X-6	19	19,0%	60
K5G5	119	3	VH3-1X-6	19	19,0%	60
K6F5	119	3	VH3-1X-6	19	19,0%	60
AL3.16	98	3	VH3-13-10	1	1,0%	117
N86P2	98	3	VH3-13-10	3	3,1%	77
N54P6	95	3	VH3-13-16	7	7,1%	77
LAMBDA HT112-1	126	4	VH4-11-2	0	0,0%	3
HY18	121	4	VH4-11-2	0	0,0%	43
mAb63	126	4	VH4-11-2	0	0,0%	45
FS-3	105	4	VH4-11-2	0	0,0%	86
FS-5	111	4	VH4-11-2	0	0,0%	86
FS-7	107	4	VH4-11-2	0	0,0%	86
FS-8	110	4	VH4-11-2	0	0,0%	86
PR-TS2	105	4	VH4-11-2	0	0,0%	85
RF-TMC	102	4	VH4-11-2	0	0,0%	85
mAb216	122	4	VH4-11-2	1	1,0%	15
mAb410.7.F91	122	4	VH4-11-2	1	1,0%	52
mAbA6H4C5	124	4	VH4-11-2	1	1,0%	15
Ab44	127	4	VH4-11-2	2	2,1%	100
6H-3C4	124	4	VH4-11-2	3	3,1%	59
FS-6	108	4	VH4-11-2	6	6,2%	86
FS-2	114	4	VH4-11-2	6	6,2%	84
HIG1	126	4	VH4-11-2	7	7,2%	62
FS-4	105	4	VH4-11-2	8	8,2%	86
SA-4A	123	4	VH4-11-2	9	9,3%	125
LES-C	119	4	VH4-11-2	10	10,3%	99
DI	78	4	VH4-11-9	16	16,5%	58
Ab26	126	4	VH4-31-4	8	8,1%	100
TS2	124	4	VH4-31-12	15	15,2%	110
265-695	115	4	VH4-11-7	16	16,5%	5
WAH	129	4	VH4-31-13	19	19,2%	93
268-D	122	4	VH4-11-8	22	22,7%	6
58P2	118	4	VH4-11-8	0	0,0%	104
mAb67	128	4	VH4-21-4	1	1,0%	45
4.L39	115	4	VH4-11-8	2	2,1%	108
mF7	111	4	VH4-31-13	3	3,0%	75

Table 2C: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
33.C9	122	4	VH4-21-5	7	7,1%	129
Pag-1	124	4	VH4-11-16	5	5,2%	50
B3	123	4	VH4-21-3	8	8,2%	53
IC4	120	4	VH4-11-8	6	6,2%	70
C6B2	127	4	VH4-31-12	4	4,0%	48
N78	118	4	VH4-11-9	11	11,3%	77
B2	109	4	VH4-11-8	12	12,4%	53
WRD2	123	4	VH4-11-12	6	6,2%	90
mAb426.4.2F20	126	4	VH4-11-8	2	2,1%	52
E54 4.58	115	4	VH4-11-8	1	1,0%	26
WRD6	123	4	VH4-11-12	10	10,3%	90
mAb426.12.3F1.4	122	4	VH4-11-9	4	4,1%	52
E54 4.2	108	4	VH4-21-6	2	2,0%	26
WIL	127	4	VH4-31-13	0	0,0%	90
COF	126	4	VH4-31-13	0	0,0%	90
LAR	122	4	VH4-31-13	2	2,0%	90
WAT	125	4	VH4-31-13	4	4,0%	90
mAb61	123	4	VH4-31-13	5	5,1%	45
WAG	127	4	VH4-31-4	0	0,0%	90
RF-SJ4	108	4	VH4-31-12	2	2,0%	85
E54 4.4	110	4	VH4-11-7	0	0,0%	26
E55 4.A1	108	4	VH4-11-7	0	0,0%	26
PR-SJ1	103	4	VH4-11-7	1	1,0%	85
E54 4.23	111	4	VH4-11-7	1	1,0%	26
CLL7 7-2	97	4	VH4-11-12	0	0,0%	29
37P1	95	4	VH4-11-12	0	0,0%	104
ALL52 30-2	91	4	VH4-31-12	4	4,0%	29
EBV-21	98	5	VH5-12-1	0	0,0%	13
CB-4	98	5	VH5-12-1	0	0,0%	13
CLL-12	98	5	VH5-12-1	0	0,0%	13
L3-4	98	5	VH5-12-1	0	0,0%	13
CLL11	98	5	VH5-12-1	0	0,0%	17
CORD3	98	5	VH5-12-1	0	0,0%	17
CORD4	98	5	VH5-12-1	0	0,0%	17
CORD8	98	5	VH5-12-1	0	0,0%	17
CORD9	98	5	VH5-12-1	0	0,0%	17

Table 2C: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
CD+1	98	5	VH5-12-1	0	0,0%	17
CD+3	98	5	VH5-12-1	0	0,0%	17
CD+4	98	5	VH5-12-1	0	0,0%	17
CD-1	98	5	VH5-12-1	0	0,0%	17
CD-5	98	5	VH5-12-1	0	0,0%	17
VERG14	98	5	VH5-12-1	0	0,0%	17
PBL1	98	5	VH5-12-1	0	0,0%	17
PBL10	98	5	VH5-12-1	0	0,0%	17
STRAb SA-1A	127	5	VH5-12-1	0	0,0%	125
DOB'	122	5	VH5-12-1	0	0,0%	97
VERG5	98	5	VH5-12-1	0	0,0%	17
PBL2	98	5	VH5-12-1	1	1,0%	17
Tu16	119	5	VH5-12-1	1	1,0%	49
PBL12	98	5	VH5-12-1	1	1,0%	17
CD+2	98	5	VH5-12-1	1	1,0%	17
CORD10	98	5	VH5-12-1	1	1,0%	17
PBL9	98	5	VH5-12-1	1	1,0%	17
CORD2	98	5	VH5-12-1	2	2,0%	17
PBL6	98	5	VH5-12-1	2	2,0%	17
CORD5	98	5	VH5-12-1	2	2,0%	17
CD-2	98	5	VH5-12-1	2	2,0%	17
CORD1	98	5	VH5-12-1	2	2,0%	17
CD-3	98	5	VH5-12-1	3	3,1%	17
VERG4	98	5	VH5-12-1	3	3,1%	17
PBL13	98	5	VH5-12-1	3	3,1%	17
PBL7	98	5	VH5-12-1	3	3,1%	17
HAN	119	5	VH5-12-1	3	3,1%	97
VERG3	98	5	VH5-12-1	3	3,1%	17
PBL3	98	5	VH5-12-1	3	3,1%	17
VERG7	98	5	VH5-12-1	3	3,1%	17
PBL5	94	5	VH5-12-1	0	0,0%	17
CD-4	98	5	VH5-12-1	4	4,1%	17
CLL10	98	5	VH5-12-1	4	4,1%	17
PBL11	98	5	VH5-12-1	4	4,1%	17
CORD6	98	5	VH5-12-1	4	4,1%	17
VERG2	98	5	VH5-12-1	5	5,1%	17

Table 2C: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
83P2	119	5	VH5-12-1	0	0,0%	103
VERG9	98	5	VH5-12-1	6	6,1%	17
CLL6	98	5	VH5-12-1	6	6,1%	17
PBL8	98	5	VH5-12-1	7	7,1%	17
Ab2022	120	5	VH5-12-1	3	3,1%	100
CAV	127	5	VH5-12-4	0	0,0%	97
HOW'	120	5	VH5-12-4	0	0,0%	97
PET	127	5	VH5-12-4	0	0,0%	97
ANG	121	5	VH5-12-4	0	0,0%	97
KER	121	5	VH5-12-4	0	0,0%	97
5.M13	118	5	VH5-12-4	0	0,0%	107
Au2.1	118	5	VH5-12-4	1	1,0%	49
WS1	126	5	VH5-12-1	9	9,2%	110
TD Vn	98	5	VH5-12-4	1	1,0%	16
TEL13	116	5	VH5-12-1	9	9,2%	73
E55 5.237	112	5	VH5-12-4	2	2,0%	26
VERG1	98	5	VH5-12-1	10	10,2%	17
CD4-74	117	5	VH5-12-1	10	10,2%	42
257-D	125	5	VH5-12-1	11	11,2%	6
CLL4	98	5	VH5-12-1	11	11,2%	17
CLL8	98	5	VH5-12-1	11	11,2%	17
Ab2	124	5	VH5-12-1	12	12,2%	120
Vh383ex	98	5	VH5-12-1	12	12,2%	120
CLL3	98	5	VH5-12-2	11	11,2%	17
Au59.1	122	5	VH5-12-1	12	12,2%	49
TEL16	117	5	VH5-12-1	12	12,2%	73
M61	104	5	VH5-12-1	0	0,0%	103
TuO	99	5	VH5-12-1	5	5,1%	49
P2-51	122	5	VH5-12-1	13	13,3%	121
P2-54	122	5	VH5-12-1	11	11,2%	121
P1-56	119	5	VH5-12-1	9	9,2%	121
P2-53	122	5	VH5-12-1	10	10,2%	121
P1-51	123	5	VH5-12-1	19	19,4%	121
P1-54	123	5	VH5-12-1	3	3,1%	121
P3-69	127	5	VH5-12-1	4	4,1%	121
P3-9	119	5	VH5-12-1	4	4,1%	121

Table 2C: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
1-185-37	125	5	VH5-12-4	0	0,0%	124
1-187-29	125	5	VH5-12-4	0	0,0%	124
P1-58	128	5	VH5-12-4	10	10,2%	121
P2-57	118	5	VH5-12-4	3	3,1%	121
P2-55	123	5	VH5-12-1	5	5,1%	121
P2-56	123	5	VH5-12-1	20	20,4%	121
P2-52	122	5	VH5-12-1	11	11,2%	121
P3-60	122	5	VH5-12-1	8	8,2%	121
P1-57	123	5	VH5-12-1	4	4,1%	121
P1-55	122	5	VH5-12-1	14	14,3%	121
MD3-4	128	5	VH5-12-4	12	12,2%	5
P1-52	121	5	VH5-12-1	11	11,2%	121
CLL5	98	5	VH5-12-1	13	13,3%	17
CLL7	98	5	VH5-12-1	14	14,3%	17
L2F10	100	5	VH5-12-1	1	1,0%	46
L3B6	98	5	VH5-12-1	1	1,0%	46
VH6.A12	119	6	VH6-35-1	13	12,9%	122
s5A9	102	6	VH6-35-1	1	1,0%	46
s6G4	99	6	VH6-35-1	1	1,0%	46
ss3	99	6	VH6-35-1	1	1,0%	46
6-1G1	101	6	VH6-35-1	0	0,0%	14
F19L16	107	6	VH6-35-1	0	0,0%	68
L16	120	6	VH6-35-1	0	0,0%	69
M71	121	6	VH6-35-1	0	0,0%	103
ML1	120	6	VH6-35-1	0	0,0%	69
F19ML1	107	6	VH6-35-1	0	0,0%	68
15P1	127	6	VH6-35-1	0	0,0%	104
VH6.N1	121	6	VH6-35-1	0	0,0%	122
VH6.N11	123	6	VH6-35-1	0	0,0%	122
VH6.N12	123	6	VH6-35-1	0	0,0%	122
VH6.N2	125	6	VH6-35-1	0	0,0%	122
VH6.N5	125	6	VH6-35-1	0	0,0%	122
VH6.N6	127	6	VH6-35-1	0	0,0%	122
VH6.N7	126	6	VH6-35-1	0	0,0%	122
VH6.N8	123	6	VH6-35-1	0	0,0%	122
VH6.N9	123	6	VH6-35-1	0	0,0%	122

Table 2C: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
VH6.N10	123	6	VH6-35-1	0	0,0%	122
VH6.A3	123	6	VH6-35-1	0	0,0%	122
VH6.A1	124	6	VH6-35-1	0	0,0%	122
VH6.A4	120	6	VH6-35-1	0	0,0%	122
E55 6.16	116	6	VH6-35-1	0	0,0%	26
E55 6.17	120	6	VH6-35-1	0	0,0%	26
E55 6.6	120	6	VH6-35-1	0	0,0%	26
VHGL 6.3	102	6	VH6-35-1	0	0,0%	26
CB-201	118	6	VH6-35-1	0	0,0%	109
VH6.N4	122	6	VH6-35-1	0	0,0%	122
E54 6.4	109	6	VH6-35-1	1	1,0%	26
VH6.A6	126	6	VH6-35-1	1	1,0%	122
E55 6.14	120	6	VH6-35-1	1	1,0%	26
E54 6.6	107	6	VH6-35-1	1	1,0%	26
E55 6.10	112	6	VH6-35-1	1	1,0%	26
E54 6.1	107	6	VH6-35-1	2	2,0%	26
E55 6.13	120	6	VH6-35-1	2	2,0%	26
E55 6.3	120	6	VH6-35-1	2	2,0%	26
E55 6.7	116	6	VH6-35-1	2	2,0%	26
E55 6.2	120	6	VH6-35-1	2	2,0%	26
E55 6.X	111	6	VH6-35-1	2	2,0%	26
E55 6.11	111	6	VH6-35-1	3	3,0%	26
VH6.A11	118	6	VH6-35-1	3	3,0%	122
A10	107	6	VH6-35-1	3	3,0%	68
E55 6.1	120	6	VH6-35-1	4	4,0%	26
FK-001	124	6	VH6-35-1	4	4,0%	65
VH6.A5	121	6	VH6-35-1	4	4,0%	122
VH6.A7	123	6	VH6-35-1	4	4,0%	122
HBp2	119	6	VH6-35-1	4	4,0%	4
Au46.2	123	6	VH6-35-1	5	5,0%	49
A431	106	6	VH6-35-1	5	5,0%	68
VH6.A2	120	6	VH6-35-1	5	5,0%	122
VH6.A9	125	6	VH6-35-1	8	7,9%	122
VH6.A8	118	6	VH6-35-1	10	9,9%	122
VH6-FF3	118	6	VH6-35-1	2	2,0%	123
VH6.A10	126	6	VH6-35-1	12	11,9%	122

Table 2C: (continued)

Name[1]	aa[2]	Computed family[3]	Germline gene[4]	Diff. to germline[5]	% diff. to germline[6]	Reference[7]
VH6-EB10	117	6	VH6-35-1	3	3,0%	123
VH6-E6	119	6	VH6-35-1	6	5,9%	123
VH6-FE2	121	6	VH6-35-1	6	5,9%	123
VH6-EE6	116	6	VH6-35-1	6	5,9%	123
VH6-FD10	118	6	VH6-35-1	6	5,9%	123
VH6-EX8	113	6	VH6-35-1	6	5,9%	123
VH6-FG9	121	6	VH6-35-1	8	7,9%	123
VH6-E5	116	6	VH6-35-1	9	8,9%	123
VH6-EC8	122	6	VH6-35-1	9	8,9%	123
VH6-E10	120	6	VH6-35-1	10	9,9%	123
VH6-FF11	122	6	VH6-35-1	11	10,9%	123
VH6-FD2	115	6	VH6-35-1	11	10,9%	123
CLL10 17-2	88	6	VH6-35-1	4	4,0%	29
VH6-BB11	94	6	VH6-35-1	4	4,0%	123
VH6-B41	93	6	VH6-35-1	7	6,9%	123
JU17	102	6	VH6-35-1	3	3,0%	114
VH6-BD9	96	6	VH6-35-1	11	10,9%	123
VH6-BB9	94	6	VH6-35-1	12	11,9%	123

Table 3A: assignment of rearranged V kappa sequences to their germline counterparts

Family[1]	Name	Rearranged[2]	Sum
1	Vk1-1	28	
1	Vk1-2	0	
1	Vk1-3	1	
1	Vk1-4	0	
1	Vk1-5	7	
1	Vk1-6	0	
1	Vk1-7	0	
1	Vk1-8	2	
1	Vk1-9	9	
1	Vk1-10	0	
1	Vk1-11	1	
1	Vk1-12	7	
1	Vk1-13	1	
1	Vk1-14	7	
1	Vk1-15	2	
1	Vk1-16	2	
1	Vk1-17	16	
1	Vk1-18	1	
1	Vk1-19	33	
1	Vk1-20	1	
1	Vk1-21	1	
1	Vk1-22	0	
1	Vk1-23	0	*119 entries*
2	Vk2-1	0	
2	Vk2-2	1	
2	Vk2-3	0	
2	Vk2-4	0	
2	Vk2-5	0	
2	Vk2-6	16	
2	Vk2-7	0	
2	Vk2-8	0	
2	Vk2-9	1	
2	Vk2-10	0	
2	Vk2-11	7	
2	Vk2-12	0	*25 entries*
3	Vk3-1	1	
3	Vk3-2	0	

Table 3A: (continued)

Family[1]	Name	Rearranged[2]	Sum
3	Vk3-3	35	
3	Vk3-4	115	
3	Vk3-5	0	
3	Vk3-6	0	
3	Vk3-7	1	
3	Vk3-8	40	*192 entries*
4	Vk4-1	33	*33 entries*
5	Vk5-1	1	*1 entry*
6	Vk6-1	0	
6	Vk6-2	0	*0 entries*
7	Vk7-1	0	*0 entries*

Table 3B: assignment of rearranged V lambda sequences to their germline counterparts

Family[1]	Name	Rearranged[2]	Sum
1	DPL1	1	
1	DPL2	14	
1	DPL3	6	
1	DPL4	1	
1	HUMLV117	4	
1	DPL5	13	
1	DPL6	0	
1	DPL7	0	
1	DPL8	3	
1	DPL9	0	*42 entries*
2	DPL10	5	
2	VLAMBDA 2.1	0	
2	DPL11	23	
2	DPL12	15	
2	DPL13	0	
2	DPL14	0	*43 entries*
3	DPL16	10	
3	DPL23	19	
3	Humlv318	9	*38 entries*
7	DPL18	1	
7	DPL19	0	*1 entries*
8	DPL21	2	
8	HUMLV801	6	*8 entries*
9	DPL22	0	*0 entries*
unassigned	DPL24	0	*0 entries*
10	gVLX-4.4	0	*0 entries*

Table 3C: assignment of rearranged V heavy chain sequences to their germline counterparts

Family[1]	Name	Rearranged[2]	Sum
1	VH1-12-1	38	
1	VH1-12-8	2	
1	VH1-12-2	2	
1	VH1-12-9	2	
1	VH1-12-3	0	
1	VH1-12-4	0	
1	VH1-12-5	3	
1	VH1-12-6	0	
1	VH1-12-7	23	
1	VH1-13-1	1	
1	VH1-13-2	1	
1	VH1-13-3	0	
1	VH1-13-4	0	
1	VH1-13-5	0	
1	VH1-13-6	17	
1	VH1-13-7	0	
1	VH1-13-8	3	
1	VH1-13-9	0	
1	VH1-13-10	0	
1	VH1-13-11	0	
1	VH1-13-12	10	
1	VH1-13-13	0	
1	VH1-13-14	0	
1	VH1-13-15	4	
1	VH1-13-16	2	
1	VH1-13-17	0	
1	VH1-13-18	1	
1	VH1-13-19	0	
1	VH1-1X-1	1	*110 entries*
2	VH2-21-1	0	
2	VH2-31-1	0	
2	VH2-31-2	1	
2	VH2-31-3	1	
2	VH2-31-4	0	
2	VH2-31-5	2	
2	VH2-31-6	0	
2	VH2-31-7	0	

Table 3C: (continued)

Family[1]	Name	Rearranged[2]	Sum
2	VH2-31-14	1	
2	VH2-31-8	0	
2	VH2-31-9	0	
2	VH2-31-10	0	
2	VH2-31-11	1	
2	VH2-31-12	0	
2	VH2-31-13	1	*7 entries*
3	VH3-11-1	0	
3	VH3-11-2	0	
3	VH3-11-3	5	
3	VH3-11-4	0	
3	VH3-11-5	1	
3	VH3-11-6	1	
3	VH3-11-7	0	
3	VH3-11-8	5	
3	VH3-13-1	9	
3	VH3-13-2	3	
3	VH3-13-3	0	
3	VH3-13-4	0	
3	VH3-13-5	0	
3	VH3-13-6	0	
3	VH3-13-7	32	
3	VH3-13-8	4	
3	VH3-13-9	0	
3	VH3-13-10	46	
3	VH3-13-11	0	
3	VH3-13-12	11	
3	VH3-13-13	17	
3	VH3-13-14	8	
3	VH3-13-15	4	
3	VH3-13-16	3	
3	VH3-13-17	2	
3	VH3-13-18	1	
3	VH3-13-19	13	
3	VH3-13-20	1	
3	VH3-13-21	1	
3	VH3-13-22	0	

Table 3C: (continued)

Family[1]	Name	Rearranged[2]	Sum
3	VH3-13-23	0	
3	VH3-13-24	4	
3	VH3-13-25	1	
3	VH3-13-26	6	
3	VH3-14-1	1	
3	VH3-14-4	15	
3	VH3-14-2	0	
3	VH3-14-3	0	
3	VH3-1X-1	0	
3	VH3-1X-2	0	
3	VH3-1X-3	6	
3	VH3-1X-4	0	
3	VH3-1X-5	0	
3	VH3-1X-6	11	
3	VH3-1X-7	0	
3	VH3-1X-8	1	
3	VH3-1X-9	0	*212 entries*
4	VH4-11-1	0	
4	VH4-11-2	20	
4	VH4-11-3	0	
4	VH4-11-4	0	
4	VH4-11-5	0	
4	VH4-11-6	0	
4	VH4-11-7	5	
4	VH4-11-8	7	
4	VH4-11-9	3	
4	VH4-11-10	0	
4	VH4-11-11	0	
4	VH4-11-12	4	
4	VH4-11-13	0	
4	VH4-11-14	0	
4	VH4-11-15	0	
4	VH4-11-16	1	
4	VH4-21-1	0	
4	VH4-21-2	0	
4	VH4-21-3	1	
4	VH4-21-4	1	

Table 3C: (continued)

Family[1]	Name	Rearranged[2]	Sum
4	VH4-21-5	1	
4	VH4-21-6	1	
4	VH4-21-7	0	
4	VH4-21-8	0	
4	VH4-21-9	0	
4	VH4-31-1	0	
4	VH4-31-2	0	
4	VH4-31-3	0	
4	VH4-31-4	2	
4	VH4-31-5	0	
4	VH4-31-6	0	
4	VH4-31-7	0	
4	VH4-31-8	0	
4	VH4-31-9	0	
4	VH4-31-10	0	
4	VH4-31-11	0	
4	VH4-31-12	4	
4	VH4-31-13	7	
4	VH4-31-14	0	
4	VH4-31-15	0	
4	VH4-31-16	0	
4	VH4-31-17	0	
4	VH4-31-18	0	
4	VH4-31-19	0	
4	VH4-31-20	0	*57 entries*
5	VH5-12-1	82	
5	VH5-12-2	1	
5	VH5-12-3	0	
5	VH5-12-4	14	*97 entries*
6	VH6-35-1	74	*74 entries*

Table 4A: Analysis of V kappa subgroup 1

amino acid[1]	Framework I															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
A		1							1				102		1	
B			1			1										
C														1		
D	64															
E	8		14												1	
F									1	6				1		
G																105
H																
I		65													4	
K			1													
L		6		21							96		1			
M	1			66												
N																
P								103		1		2			1	
Q			62			88					1					
R																
S							89		102	80		103		103		
T		1			88					18						
V		1	9								8		2		98	
W																
X	1															
Y																
-																
unknown (?)																
not sequenced	31	31	18	18	17	16	16	2	1							
sum of seq[2]	74	74	87	87	88	89	89	103	104	105	105	105	105	105	105	105
oomcaa[3]	64	65	62	66	88	88	89	103	102	80	96	103	102	103	98	105
mcaa[4]	D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G
rel. oomcaa[5]	86%	88%	71%	76%	100%	99%	100%	100%	98%	76%	91%	98%	97%	98%	93%	100%
pos occupied[6]	4	5	5	2	1	2	1	1	3	4	3	2	3	3	5	1

Table 4A: Analysis of V kappa subgroup 1

amino acid[1]	17	18	19	20	21	22	23	24	25	26	27	A	B	C	D
A			1	1		1			103						
B											1				
C							105								
D	101														
E	2							1	1		2				
F					2										
G										1					
H											1				
I			6	4	101	1									
K								2			1				
L								1							
M															
N										1					
P															
Q								20			100				
R		94						81							
S		5		1						102					
T		6		99		103			1	1					
V			98		2										
W															
X	1														
Y	1														
-												105	105	105	105
unknown (?)															
not sequenced															
sum of seq[2]	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
oomcaa[3]	101	94	98	99	101	103	105	81	103	102	100	105	105	105	105
mcaa[4]	D	R	V	T	I	T	C	R	A	S	Q	-	-	-	-
rel. oomcaa[5]	96%	90%	93%	94%	96%	98%	100%	77%	98%	97%	95%	100%	100%	100%	100%
pos occupied[6]	4	3	3	4	3	3	1	5	3	4	5	1	1	1	1

Table 4A: Analysis of V kappa subgroup 1

	CDRI														
amino acid[1]	E	F	28	29	30	31	32	33	34	35	36	37	38	39	40
A					1	1		1	42						
B												1	1		
C							1								
D			25		1	5	7					1			
E							1					2			
F				1	1		7				6				
G			25		7	3			4						
H					1	2	2		1			2			
I				98	1	4			1						
K						7								95	
L					2	1		101							
M															
N			6		16	42			50						
P															102
Q												98	103	2	
R					16	3	2							3	1
S			41	2	57	32	3	1	1						1
T			7			4			4					1	
V			1	4	1			1							
W							21			104					
X									1						
Y					1		60				98				
-	105	105													
unknown (?)														3	
not sequenced						1	1	1	1	1	1	1	1	1	1
sum of seq[2]	105	105	105	105	105	104	104	104	104	104	104	104	104	104	104
oomcaa[3]	105	105	41	98	57	42	60	101	50	104	98	98	103	95	102
mcaa[4]	-	-	S	I	S	N	Y	L	N	W	Y	Q	Q	K	P
rel. oomcaa[5]	100%	100%	39%	93%	54%	40%	58%	97%	48%	100%	94%	94%	99%	91%	98%
pos occupied[6]	1	1	6	4	12	11	9	4	8	1	2	5	2	4	3

Table 4A: Analysis of V kappa subgroup 1

	Framework II									CDR II					
amino acid[1]	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55
A			94							50	95				
B															
C															
D										21	1	1	1		
E	1	3			1	1				1		1			33
F						1			3			1			
G	100		1							9	2				
H									2						1
I		1				1		100					1		
K		95			86					16			2		5
L		1				89	103							101	
M								2							
N					10					2		1	25		
P				104						1					1
Q		1			1										62
R					3	3							1	1	2
S					1				5	1	1	99	41	2	
T		3			1					1	4	1	31		
V			9			9					1		1		
W															
X					1								1		
Y									92	1					
-															
unknown (?)	3														
not sequenced	1	1	1	1	1	1	2	3	3	2	1	1	1	1	1
sum of seq[2]	104	104	104	104	104	104	103	102	102	103	104	104	104	104	104
oomcaa[3]	100	95	94	104	86	89	103	100	92	50	95	99	41	101	62
mcaa[4]	G	K	A	P	K	L	L	I	Y	A	A	S	S	L	Q
rel. oomcaa[5]	96%	91%	90%	100%	83%	86%	100%	98%	90%	49%	91%	95%	39%	97%	60%
pos occupied[6]	2	6	3	1	8	6	1	2	4	10	6	6	9	3	6

Table 4A: Analysis of V kappa subgroup 1

amino acid[1]	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70
A	3										2	1	1	1	
B				1											
C															
D	1														67
E													1		30
F			1				103					3			
G	2	105							105	4	101		102		
H															3
I	3		4				1	3							
K	1					1									1
L								1							
M														1	
N	6														
P	1			101	2										
Q										1					
R	1					103		1		1	1			2	
S	68			2	103			98		96		100			
T	19			1		1		2		3				101	
V			99				1								1
W															
X			1								1		1		2
Y												1			1
-															
unknown (?)															
not sequenced															
sum of seq[2]	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
oomcaa[3]	68	105	99	101	103	103	103	98	105	96	101	100	102	101	67
mcaa[4]	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D
rel. oomcaa[5]	65%	100%	94%	96%	98%	98%	98%	93%	100%	91%	96%	95%	97%	96%	64%
pos occupied[6]	10	1	4	4	2	3	3	5	1	5	4	4	4	4	7

Table 4A: Analysis of V kappa subgroup 1

	Framework III														
amino acid[1]	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85
A		3				1				2				101	1
B					1				3		2				
C															
D						1					16	101			
E											83				
F	102	1	21										73		
G							4				1			2	
H															
I					99	5							17		
K															
L			81					103	1				1		
M															1
N						7	4								1
P										97					1
Q									97						
R						2	1		2						
S		2		1		86	94			4			1		
T		98		102		2	1								97
V	1		2		4			1					11		1
W															
X				1							1	2			
Y	1														
-															
unknown (?)															
not sequenced	1	1	1	1	1	1	1	1	2	2	2	2	2	2	3
sum of seq[2]	104	104	104	104	104	104	104	104	103	103	103	103	103	103	102
oomcaa[3]	102	98	81	102	99	86	94	103	97	97	83	101	73	101	97
mcaa[4]	F	T	L	T	I	S	S	L	Q	P	E	D	F	A	T
rel. oomcaa[5]	98%	94%	78%	98%	95%	83%	90%	99%	94%	94%	81%	98%	71%	98%	95%
pos occupied[5]	3	4	3	3	3	7	5	2	4	3	5	2	5	2	6

Table 4A: Analysis of V kappa subgroup 1

				CDR III												
amino acid[1]	86	87	88	89	90	91	92	93	94	95	A	B	C	D	E	F
A					1	7	1		5	1						
B				2	3											
C			102													
D							23	5	1							
E							1	1		1	1					
F		7				3			13							
G						1		1	2	1		1				
H		1		4	6	7	3	1								
I							4	1	2	1						
K	1				7		1									
L				7		6	2		18	2						
M																
N						6	31	19	1							
P									1	82	6					
Q				90	86	1	2									
R						1		2	2							
S	1					27	3	58	5	10						
T						3	1	15	25							
V									5							
W									1							
X																
Y	101	93				42	32	1	23							
-										3	82	88	89	89	89	89
unknown (?)		1														
not sequenced	2	3	3	2	2	1	1	1	1	4	16	16	16	16	16	16
sum of seq[2]	103	102	102	103	103	104	104	104	104	101	89	89	89	89	89	89
oomcaa[3]	101	93	102	90	86	42	32	58	25	82	82	88	89	89	89	89
mcaa[4]	Y	Y	C	Q	Q	Y	Y	S	T	P	-	-	-	-	-	-
rel. oomcaa[5]	98%	91%	100%	87%	83%	40%	31%	56%	24%	81%	92%	99%	100%	100%	100%	100%
pos occupied[6]	3	3	1	4	5	11	12	10	14	8	3	2	1	1	1	1

Table 4A: Analysis of V kappa subgroup 1

			Framework IV												
amino acid[1]	96	97	98	99	100	101	102	103	104	105	106	A	107	108	sum
A	1														627
B					1					1					19
C															209
D	1									15					459
E					2					65					258
F	6		86								2				451
G				87	29	87								2	894
H	2	1													40
I	5								1		72				606
K	1	1						77					79		480
L	18	1	1						22	4	2				793
M		1									5				77
N	1										1		2		232
P	6				7									1	620
Q	1				48					1					865
R	6							6					2	70	413
S	2	2													1636
T	2	82					87	3					2		1021
V	2							1	63		3				440
W	15														141
X															14
Y	16														564
-	4	1										85		1	1250
unknown (?)															7
not sequenced	16	16	18	18	18	18	18	18	19	19	20	20	20	31	589
sum of seq[2]	89	89	87	87	87	87	87	87	86	86	85	85	85	74	
oomcaa[3]	18	82	86	87	48	87	87	77	63	65	72	85	79	70	
mcaa[4]	L	T	F	G	G	G	T	K	V	E	I	-	K	R	
rel. oomcaa[5]	20%	92%	99%	100%	55%	100%	100%	89%	73%	76%	85%	100%	93%	95%	
pos occupied[6]	17	7	2	1	5	1	1	4	3	5	6	1	4	4	

Table 4B: Analysis of V kappa subgroup 2

	Framework I																				
amino acid[1]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
A																			22		
B																					
C																					
D	14																				
E	3																15				
F									1	1											
G																22					
H																					
I		8																			22
K																					
L		3		1					17		18				6						
M				15																	
N																					
P								18				18			15			22			
Q						18											7				
R																					
S							18			17										22	
T					17									21							
V		6	17	1									18								
W																					
X																					
Y																					
-																					
unknown (?)					1																
not sequenced	5	5	5	5	4	4	4	4	4	4	4	4	4	1	1						
sum of seq[2]	17	17	17	17	18	18	18	18	18	18	18	18	18	21	21	22	22	22	22	22	22
oomcaa[3]	14	8	17	15	17	18	18	18	17	17	18	18	18	21	15	22	15	22	22	22	22
mcaa[4]	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I
rel. oomcaa[5]	82%	47%	100%	88%	94%	100%	100%	100%	94%	94%	100%	100%	100%	100%	71%	100%	68%	100%	100%	100%	100%
pos occupied[6]	2	3	1	3	1	1	1	1	2	2	1	1	1	1	2	1	2	1	1	1	1

Table 4B: Analysis of V kappa subgroup 2

											CDRI										
amino acid[1]	22	23	24	25	26	27	A	B	C	D	E	F	28	29	30	31	32	33	34	35	36
A																					
B																					
C		22																			
D										1			9		1	1			11		
E																					
F															2						7
G											1			22							
H										16							1		1		
I																					
K			1													1					
L						1		22	13									22			
M									1												
N													10		7	12			9		
P																					
Q	1					21															
R			21								2										
S	21			22	22		22				19		1								
T																8					
V									8												
W										1										22	
X													1		1				1		
Y										4			1		11		21				15
-												22									
unknown (?)																					
not sequenced																					
sum of seq[2]	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22
oomcaa[3]	21	22	21	22	22	21	22	22	13	16	19	22	10	22	11	12	21	22	11	22	15
mcaa[4]	S	C	R	S	S	Q	S	L	L	H	S	-	N	G	Y	N	Y	L	D	W	Y
rel. oomcaa[5]	95%	100%	95%	100%	100%	95%	100%	100%	59%	73%	86%	100%	45%	100%	50%	55%	95%	100%	50%	100%	68%
pos occupied[6]	2	1	2	1	1	2	1	1	3	4	3	1	5	1	5	4	2	1	4	1	2

Table 4B: Analysis of V kappa subgroup 2

	Framework II													CDR II							
amino acid[1]	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57
A																			14		
B																					
C																					
D																			7		
E									1												
F																					
G					22										12				1		22
H																					
I										1		22									
K			15											5							
L	16									14	21			14	1						
M																					
N																	18				
P				22				21													
Q	6	22				22			12					1							
R			7						8	7				1				22			
S							21								2	22	2			22	
T																	1				
V											1				6						
W																					
X																					
Y													21				1				
-																					
unknown (?)																					
not sequenced							1	1	1				1	1	1						
sum of seq[2]	22	22	22	22	22	22	21	21	21	22	22	22	21	21	21	22	22	22	22	22	22
oomcaa[3]	16	22	15	22	22	22	21	21	12	14	21	22	21	14	12	22	18	22	14	22	22
mcaa[4]	L	Q	K	P	G	Q	S	P	Q	L	L	I	Y	L	G	S	N	R	A	S	G
rel. oomcaa[5]	73%	100%	68%	100%	100%	100%	100%	100%	57%	64%	95%	100%	100%	67%	57%	100%	82%	100%	64%	100%	100%
pos occupied[6]	2	1	2	1	1	1	1	1	3	3	2	1	1	4	4	1	4	1	3	1	1

Table 4B: Analysis of V kappa subgroup 2

	Framework III																				
amino acid[1]	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78
A																					
B																					
C																					
D			22				1				1		22								
E																					
F					21									22							
G							21		22		21										
H																					
I																	1	21			
K																	19				
L																21	1				
M																					
N																					
P		22																			
Q																					
R				20				1												20	
S				1		22		21		22									20	1	
T				1								22			21				1		
V	22				1																21
W																					
X																					
Y																					
-																					
unknown (?)															1						
not sequenced																1	1	1	1	1	1
sum of seq[2]	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	21	21	21	21	21	21
oomcaa[3]	22	22	22	20	21	22	21	21	22	22	21	22	22	22	21	21	19	21	20	20	21
mcaa[4]	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V
rel. oomcaa[5]	100%	100%	100%	91%	95%	100%	95%	95%	100%	100%	95%	100%	100%	100%	95%	100%	90%	100%	95%	95%	100%
pos occupied[6]	1	1	1	3	2	1	2	2	1	1	2	1	1	1	1	1	3	1	2	2	1

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Table 4B: Analysis of V kappa subgroup 2

																	CDR III				
amino acid[1]	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	A	B	C	D
A		20											14			1					
B												1			1						
C										21											
D			1	21																	
E	19		20																		
F																					
G	1					21							6			1		2			
H													1		7						
I							1									1					
K																					
L							1							12			2				
M											21										
N																					
P		1														2	16	1			
Q	1											20			13						
R														1							
S																3	2				
T														8		7					
V					21		19														
W																6					
X																					
Y								21	21												
-																		14	17	17	17
unknown (?)																					
not sequenced	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	5	5	5	5
sum of seq[2]	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	20	17	17	17	17
oomcaa[3]	19	20	20	21	21	21	19	21	21	21	21	20	14	12	13	7	16	14	17	17	17
mcaa[4]	E	A	E	D	V	G	V	Y	Y	C	M	Q	A	L	Q	T	P	-	-	-	-
rel. oomcaa[5]	90%	95%	95%	100%	100%	100%	90%	100%	100%	100%	100%	95%	67%	57%	62%	33%	80%	82%	100%	100%	100%
pos occupied[6]	3	2	2	1	1	1	3	1	1	1	1	2	3	3	3	7	3	3	1	1	1

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Table 4B: Analysis of V kappa subgroup 2

amino acid[1]	E	F	96	97	98	99	100	101	102	103	104	105	106	A	107	108	sum
					Framework IV												
A																	71
B												1					3
C																	43
D																	112
E												13					71
F			1		17												72
G						17	2	16				1					233
H																	26
I			3										14				94
K										12					13		66
L			2								11						219
M																	37
N																	56
P			1														159
Q			1				14										159
R										4						12	126
S																	325
T				17					16								140
V											5						146
W			2														31
X																	3
Y			7														123
-	17	17												13			134
unknown (?)																	2
not sequenced	5	5	5	5	5	5	6	6	6	6	6	7	8	9	9	10	211
sum of seq[2]	17	17	17	17	17	17	16	16	16	16	16	15	14	13	13	12	
oomcaa[3]	17	17	7	17	17	17	14	16	16	12	11	13	14	13	13	12	
mcaa[4]	-	-	Y	T	F	G	Q	G	T	K	L	E	I	-	K	R	
rel. oomcaa[5]	100%	100%	41%	100%	100%	100%	88%	100%	100%	75%	69%	87%	100%	100%	100%	100%	
pos occupied[6]	1	1	7	1	1	1	2	1	1	2	2	3	1	1	1	1	

Table 4C: Analysis of V kappa subgroup 3

	Framework I															
amino acid[1]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
A		5					2		27						1	
B	1															
C												2				
D	2								14							
E	76		27													
F		1												1		
G	1								82						1	152
H										1						
I		75														
K	3															
L		4	1	104			1				150		129		1	
M	5			13												
N														5		
P								124							147	
Q						123										
R					1											
S							119		3	1		150	1	141		
T		2			117					147				5	1	
V		1	89	1			1				1		22		1	
W																
X																
Y																
-																
unknown (?)																
not sequenced																
sum of seq[2]	88	88	117	118	118	123	123	124	126	149	151	152	152	152	152	152
oomcaa[3]	76	75	89	104	117	123	119	124	82	147	150	150	129	141	147	152
mcaa[4]	E	I	V	L	T	Q	S	P	G	T	L	S	L	S	P	G
rel. oomcaa[5]	86%	85%	76%	88%	99%	100%	97%	100%	65%	99%	99%	99%	85%	93%	97%	100%
pos occupied[6]	6	6	3	3	2	1	4	1	4	3	2	2	3	4	6	1

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Table 4C: Analysis of V kappa subgroup 3

																CDRI
amino acid[1]	17	18	19	20	21	22	23	24	25	26	27	A	B	C	D	E
A			178	2					166	1						
B																
C							181			1						
D	6															
E	146	1									1					
F					7	1										
G	1	1							1	1		1				
H											17					
I		1		5	2											
K		1						5								
L					173						1	1				
M																
N												9				
P																
Q											159					
R		175						176		1	1	10				
S						180			7	175		87				
T		1		174					7	2		1				
V		1	4	1					1			1				
W								1								
X																
Y						1					1					
-												72	182	182	182	182
unknown (?)											1					
not sequenced																
sum of seq[2]	153	181	182	182	182	182	181	182	182	181	181	182	182	182	182	182
oomcaa[3]	146	175	178	174	173	180	181	176	166	175	159	87	182	182	182	182
mcaa[4]	E	R	A	T	L	S	C	R	A	S	Q	S	-	-	-	-
rel. oomcaa[5]	95%	97%	98%	96%	95%	99%	100%	97%	91%	97%	88%	48%	100%	100%	100%	100%
pos occupied[6]	3	7	2	4	3	3	1	3	5	6	6	8	1	1	1	1

Table 4C: Analysis of V kappa subgroup 3

																Framewo
amino acid[1]	F	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
A				1	1			181								
B																
C																
D			1	1	2	1										
E						1							1			1
F		1				7				1						
G			2	7	3	1		2						1	184	
H			1			2				1		12	1	1		
I		24	4	1	1											
K				1	1								153			
L		8	1			1	176					3				2
M																
N			3	12	25	32										
P					1									170		
Q					1	1					183	167	1			181
R			10	3	18	16		1			1		27	5		
S		72	86	151	118	4								5		
T		1	1	3	8	1							1			
V		76	68		1		7					3		2		
W			5						185							
X																
Y				1	1	115				183						
-	182															
unknown (?)											1					
not sequenced																
sum of seq[2]	182	182	182	181	181	182	183	184	185	185	185	185	184	184	184	184
oomcaa[3]	182	76	86	151	118	115	176	181	185	183	183	167	153	170	184	181
mcaa[4]	-	V	S	S	S	Y	L	A	W	Y	Q	Q	K	P	G	Q
rel. oomcaa[5]	100%	42%	47%	83%	65%	63%	96%	98%	100%	99%	99%	90%	83%	92%	100%	98%
pos occupied[6]	1	6	11	10	13	12	2	3	1	3	2	4	6	6	1	3

Table 4C: Analysis of V kappa subgroup 3

	·rk II							CDR II								
amino acid[1]	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58
A	176							4	147				176	1		
B																
C									1							
D								43					2		4	
E																
F				1		1	4									
G								125					2	10	179	
H							9		1							
I						178								1		168
K			1								7	1				
L		1		179	174	1										
M						3					1					
N			1					1			53			2		
P	5	184								2			2	2		
Q							1									
R			182					1			4	180				
S							3	6	4	179	74	1		5		
T	3								11	2	44			164		2
V				3	9			3	19				3			15
W							1					1				
X																
Y							165								2	
-																
unknown (?)			1													
not sequenced																
sum of seq[7]	184	185	185	183	183	183	183	183	183	183	183	183	185	185	185	185
oomcaa[3]	176	184	182	179	174	178	165	125	147	179	74	180	176	164	179	168
mcaa[4]	A	P	R	L	L	I	Y	G	A	S	S	R	A	T	G	I
rel. oomcaa[5]	96%	99%	98%	98%	95%	97%	90%	68%	80%	98%	40%	98%	95%	89%	97%	91%
pos occupied[6]	3	2	3	3	2	4	6	7	6	3	6	4	5	7	3	3

Table 4C: Analysis of V kappa subgroup 3

	Framework III															
amino acid[1]	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74
A		68						3		5	3	1		3		
B																
C																
D		112				1						152				
E								1		1		30				
F				183									183		2	
G						184	3	178	–	177						
H		1														
I				1										1		3
K			1													
L				1											182	
M								1								
N		1												1		
P	177															
Q												1				
R			182		2		1				2					
S	7				180		179		185		3			7		2
T	1		2		3		2				177			172		179
V		3						1		1						
W										1						
X																
Y													1			
-																
unknown (?)								1								
not sequenced																
sum of seq[2]	185	185	185	185	185	185	185	185	185	185	185	184	184	184	184	184
oomcaa[3]	177	112	182	183	180	184	179	178	185	177	177	152	183	172	182	179
mcaa[4]	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	T
rel. oomcaa[5]	96%	61%	98%	99%	97%	99%	97%	96%	100%	96%	96%	83%	99%	93%	99%	97%
pos occupied[6]	3	5	3	3	3	2	4	5	1	5	4	4	2	5	2	3

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Table 4C: Analysis of V kappa subgroup 3

amino acid[1]	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90
A							3			174						
B					1											
C									2				1	182		
D			1				3	182								
E					149		175									2
F		1							178		2	1	4			
G			3					1		2						
H											1				1	7
I	178							1	1		9					
K							1									
L				178		1			1		7		1			1
M										1	5					
N	1	5														
P						149										
Q					34									1	181	155
R		1	111							3						1
S		169	65			34			1				2			
T		8	4							1						8
V	4			6					1	3	159					7
W																
X																
Y	1										1	183	176		1	2
-																
unknown (?)																
not sequenced																
sum of seq[2]	184	184	184	184	184	184	182	184	184	184	184	184	184	183	183	183
oomcaa[3]	178	169	111	178	149	149	175	182	178	174	159	183	176	182	181	155
mcaa[4]	I	S	R	L	E	P	E	D	F	A	V	Y	Y	C	Q	Q
rel. oomcaa[5]	97%	92%	60%	97%	81%	81%	96%	99%	97%	95%	86%	99%	96%	99%	99%	85%
pos occupied[6]	4	5	5	2	3	3	4	3	6	6	7	2	5	2	3	8

Table 4C: Analysis of V kappa subgroup 3

	CDR III															
amino acid[1]	91	92	93	94	95	A	B	C	D	E	F	96	97	98	99	100
A		1	8	3	3											1
B																
C	2			1								2				
D		8	5										1			
E		2										1				
F	5		2									7		166		
G	1	104	15		1	1	2					1			166	41
H	4	1										2				
I			1			1						4				
K			2			1						1				1
L				2	7	5						42				
M		1			1	2										
N		28	71									1				
P				1	139	24						7	2			9
Q	1		1		3	1						3				114
R	34	2	3		2	2						19				
S	2	33	58	102	15	2						1	8			
T		2	13	1	1	2						1	154			
V					3	1						2				
W				69								24				
X																
Y	134	1	1									43				
-			3	3	7	127	167	169	169	169	169	8	1	1	1	1
unknown (?)																
not sequenced						14	14	14	14	14	14	14	17	16	16	16
sum of seq[2]	183	183	183	182	182	169	169	169	169	169	169	169	166	167	167	167
oomcaa[3]	134	104	71	102	139	127	167	169	169	169	169	43	154	166	166	114
mcaa[4]	Y	G	N	S	P	-	-	-	-	-	-	Y	T	F	G	Q
rel. oomcaa[5]	73%	57%	39%	56%	76%	75%	99%	100%	100%	100%	100%	25%	93%	99%	99%	68%
pos occupied[6]	8	11	13	8	11	12	2	1	1	1	1	18	5	2	2	6

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Table 4C: Analysis of V kappa subgroup 3

	Framework IV									
amino acid[1]	101	102	103	104	105	106	A	107	108	sum
A										1345
B										2
C										375
D					23					564
E			3		141					759
F						6				765
G	166								1	1804
H					1					64
I						143				803
K			152					157		489
L				54		1			2	1596
M						3				36
N		1						3		255
P		1		1						1147
Q			1		1					1314
R			9			2		4	134	1326
S		2								2629
T		162	1					1		1593
V				111		11				646
W										287
X										
Y			1							1014
-	1	1	1	1	1	1	166	1	1	2151
unknown (?)										4
not sequenced	16	16	15	16	16	16	17	17	45	337
sum of seq[2]	167	167	168	167	167	167	166	166	138	
oomcaa[3]	166	162	152	111	141	143	166	157	134	
mcaa[4]	G	T	K	V	E	I	-	K	R	
rel. oomcaa[5]	99%	97%	90%	66%	84%	86%	100%	95%	97%	
pos occupied[6]	2	5	7	4	5	7	1	5	4	

Table 4D: Analysis of V kappa subgroup 4

	Framework I																	
amino acid[1]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
A												24					1	
B																		
C										1						1		
D	25								26									
E																	25	
F																		
G												1				24		
H																		
I		26																
K						1												
L				1							26				26			
M				24														
N	1																	
P								26				1						
Q			1			25												
R																		26
S							26			25				26		1		
T					26													
V			25	1									26					
W																		
X																		
Y																		
-																		
unknown (?)																		
not sequenced	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
sum of seq[2]	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26
oomcaa[3]	25	26	25	24	26	25	26	26	26	25	26	24	26	26	26	24	25	26
mcaa[4]	D	I	V	M	T	Q	S	P	D	S	L	A	V	S	L	G	E	R
rel. oomcaa[5]	96%	100%	96%	92%	100%	96%	100%	100%	100%	96%	100%	92%	100%	100%	100%	92%	96%	100%
pos occupied[6]	2	1	2	3	1	2	1	1	1	2	1	3	1	1	1	3	2	1

Table 4D: Analysis of V kappa subgroup 4

						CDRI												
amino acid[1]	19	20	21	22	23	24	25	26	27	A	B	C	D	E	F	28	29	30
A	26						1				1							
B																		
C					33													
D											1		1			1		
E																		
F																		
G																		
H																		
I			26								1							
K						33										2		30
L											2	31						
M																		
N				26												30	31	1
P							1								1			
Q									32									1
R									1								1	1
S							31	33		33				32	32		1	
T		26												1				
V											28	2						
W																		
X																		
Y													32					
-																		
unknown (?)																		
not sequenced	7	7	7	7														
sum of seq[2]	26	26	26	26	33	33	33	33	33	33	33	33	33	33	33	33	33	33
oomcaa[3]	26	26	26	26	33	33	31	33	32	33	28	31	32	32	32	30	31	30
mcaa[4]	A	T	I	N	C	K	S	S	Q	S	V	L	Y	S	S	N	N	K
rel. oomcaa[5]	100%	100%	100%	100%	100%	100%	94%	100%	97%	100%	85%	94%	97%	97%	97%	91%	94%	91%
pos occupied[6]	1	1	1	1	1	1	3	1	2	1	5	2	2	2	2	3	3	4

Table 4D: Analysis of V kappa subgroup 4

					Framework II													
amino acid[1]	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
A				32						2								
B																		
C																		
D																		
E											1							
F																		
G											32							
H						2												
I																		32
K									33						32			
L			33													29	33	
M																		1
N	33																	
P										31			31	33				
Q							32	33				32						
R							1					1			1			
S													2					
T				1														
V																4		
W					33													
X																		
Y		33				31												
-																		
unknown (?)																		
not sequenced																		
sum of seq[2]	33	33	33	33	33	33	33	33	33	33	33	33	33	33	33	33	33	33
oomcaa[3]	33	33	33	32	33	31	32	33	33	31	32	32	31	33	32	29	33	32
mcaa[4]	N	Y	L	A	W	Y	Q	Q	K	P	G	Q	P	P	K	L	L	I
rel. oomcaa[5]	100%	100%	100%	97%	100%	94%	97%	100%	100%	94%	97%	97%	94%	100%	97%	88%	100%	97%
pos occupied[6]	1	1	1	2	1	2	2	1	1	2	2	2	2	1	2	2	1	2

Table 4D: Analysis of V kappa subgroup 4

		CDR II																
amino acid[1]	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66
A			30															
B																		
C																		
D												33						
E							32											
F														33				
G									33						1	33		33
H																		
I					1													
K																		
L																		
M																		
N					2													
P				1							33		1					
Q																		
R						33							32					
S			1	31	1			33							32		33	
T			2	1	29													
V							1			33								
W		33																
X																		
Y	33																	
-																		
unknown (?)																		
not sequenced																		
sum of seq[2]	33	33	33	33	33	33	33	33	33	33	33	33	33	33	33	33	33	33
oomcaa[3]	33	33	30	31	29	33	32	33	33	33	33	33	32	33	32	33	33	33
mcaa[4]	Y	W	A	S	T	R	E	S	G	V	P	D	R	F	S	G	S	G
rel. oomcaa[5]	100%	100%	91%	94%	88%	100%	97%	100%	100%	100%	100%	100%	97%	100%	97%	100%	100%	100%
pos occupied[6]	1	1	3	3	4	1	2	1	1	1	1	1	2	1	2	1	1	1

Table 4D: Analysis of V kappa subgroup 4

	Framework III																	
amino acid'	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84
A														33				32
B																		
C																		
D				32												33		
E															33			
F					32													
G		33		1														1
H																		
I									33									
K																		
L							33					32						
M												1						
N										2	1							
P																		
Q													32					
R													1					
S	33									30	32							
T			33			33		33		1								
V					1												33	
W																		
X																		
Y																		
-																		
unknown (?)																		
not sequenced																		
sum of seq'	33	33	33	33	33	33	33	33	33	33	33	33	33	33	33	33	33	33
oomcaa'	33	33	33	32	32	33	33	33	33	30	32	32	32	33	33	33	33	32
mcaa'	S	G	T	D	F	T	L	T	I	S	S	L	Q	A	E	D	V	A
rel. oomcaa'	100%	100%	100%	97%	97%	100%	100%	100%	100%	91%	97%	97%	97%	100%	100%	100%	100%	97%
pos occupied'	1	1	1	2	2	1	1	1	1	3	2	2	2	1	1	1	1	2

Table 4D: Analysis of V kappa subgroup 4

					CDR III													
amino acid[1]	85	86	87	88	89	90	91	92	93	94	95	A	B	C	D	E	F	96
A										1								
B																		
C				33														
D								1	1									
E																		
F			1					1										
G									2									
H			1		3													
I										2								
K																		
L						1		2		1	3							1
M																		
N									4	4								
P										1	29	1						4
Q					30	32					1							1
R									1			1						2
S							2		23	2								1
T									2	22								
V	33																	
W																		2
X																		
Y		33	31				31	29										1
-												13	15	15	15	15	15	3
unknown (?)																		
not sequenced												18	18	18	18	18	18	18
sum of seq[2]	33	33	33	33	33	33	33	33	33	33	33	15	15	15	15	15	15	15
oomcaa[3]	33	33	31	33	30	32	31	29	23	22	29	13	15	15	15	15	15	4
mcaa[4]	V	Y	Y	C	Q	Q	Y	Y	S	T	P	-	-	-	-	-	-	P
rel. oomcaa[5]	100%	100%	94%	100%	91%	97%	94%	88%	70%	67%	88%	87%	100%	100%	100%	100%	100%	27%
pos occupied[6]	1	1	3	1	2	2	2	4	6	7	3	3	1	1	1	1	1	8

Table 4D: Analysis of V kappa subgroup 4

amino acid[1]	97	98	99	100	101	102	103	104	105	106	A	107	108	sum
		Framework IV												
A														183
B														
C														68
D														154
E									14					105
F		15												82
G			15	4	15									228
H														6
I										14				135
K							14					13		158
L								4						258
M	1													27
N												1		136
P						1								195
Q				11				1						264
R							1		1			1	11	116
S	2									1				499
T	12					14								236
V								9						196
W								1						69
X														
Y														254
-											15			106
unknown (?)														
not sequenced	18	18	18	18	18	18	18	18	18	18	18	18	22	518
sum of seq[2]	15	15	15	15	15	15	15	15	15	15	15	15	11	
oomcaa[3]	12	15	15	11	15	14	14	9	14	14	15	13	11	
mcaa[4]	T	F	G	Q	G	T	K	V	E	I	-	K	R	
rel. oomcaa[5]	80%	100%	100%	73%	100%	93%	93%	60%	93%	93%	100%	87%	100%	
pos occupied[6]	3	1	1	2	1	2	2	4	2	2	1	3	1	

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Table 5A: Analysis of V lambda subgroup 1

	Framework I																		
amino acid[1]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
A											19		18	20					
B																			
C																			
D																			
E																		1	
F																			
G													22			42			
H	2																		
I			1								1								
K																		14	
L			1	41							1								
M																			
N																			
P							41	41						1	41				
Q	22		1			41											42		
R																		25	
S		39							41			41			1			1	
T					41									19				1	
V		1	38								20		1	1					42
W																			
X																			
Y																			
Z	16																		
-										41									
unknown (?)																			
not sequenced	2	2	1	1	1	1	1	1	1	1	1	1	1	1					
sum of seq[2]	40	40	41	41	41	41	41	41	41	41	41	41	41	41	42	42	42	42	42
oomcaa[3]	22	39	38	41	41	41	41	41	41	41	20	41	22	20	41	42	42	25	42
mcaa[4]	Q	S	V	L	T	Q	P	P	S	-	V	S	G	A	P	G	Q	R	V
rel. oomcaa[5]	55%	98%	93%	100%	100%	100%	100%	100%	100%	100%	49%	100%	54%	49%	98%	100%	100%	60%	100%
pos occupied[6]	3	2	4	1	1	1	1	1	1	1	4	1	3	4	2	1	1	5	1

Table 5A: Analysis of V lambda subgroup 1

amino acid[1]	20	21	22	23	24	25	26	27	D	E	28	29	30	31	A	32	33	34	35
					CDRI														
A	2							1				2	2			1			
B																			
C				42															
D										3			3	1		3		1	
E													1						
F					1				1						1	1			
G						42	3	1			2	39	4	2					
H														2		2		2	
I	1	41								1	37							1	
K										1			1						
L		1									1								
M											1								
N								2	1	37			13	31	2		1	9	
P																1			
Q																1			
R							1	1					5						
S	1		42		38		34	34	38				13	1	1	3		19	
T	38				3		4	3	2			1		1		7		2	
V											1					2	40		
W																			42
X																			
Y														4	1	20		7	
Z																			
-															36				
unknown (?)																			
not sequenced															1	1	1	1	
sum of seq[2]	42	42	42	42	42	42	42	42	42	42	42	42	42	42	41	41	41	41	42
oomcaa[3]	38	41	42	42	38	42	34	34	38	37	37	39	13	31	36	20	40	19	42
mcaa[4]	T	I	S	C	S	G	S	S	S	N	I	G	N	N	-	Y	V	S	W
rel. oomcaa[5]	90%	98%	100%	100%	90%	100%	81%	81%	90%	88%	88%	93%	31%	74%	88%	49%	98%	46%	100%
pos occupied[6]	4	2	1	1	3	1	4	6	4	4	5	3	8	7	5	10	2	7	1

Table 5A: Analysis of V lambda subgroup 1

	Framework II																		
amino acid[1]	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54
A							4	40									1		
B																			
C																			
D						1									13	10	8		
E										2					5			1	
F	1			4										1					
G						39									1				
H	1	1	6	1										1				1	
I													40		1				
K							1			35					1	1		18	
L			1	31							41	40						1	1
M							1						1					1	
N										1					3	28	30	2	
P					42	1			42										
Q		39	34															15	
R		2		1		1				4					7			2	40
S								1							9	2	3	1	
T							36	1							1				
V			1	5							1	2	1						
W																			1
X																			
Y	40													40	1	1			
Z																			
-																			
unknown (?)																			
not sequenced																			
sum of seq[2]	42	42	42	42	42	42	42	42	42	42	42	42	42	42	42	42	42	42	42
oomcaa[3]	40	39	34	31	42	39	36	40	42	35	41	40	40	40	13	28	30	18	40
mcaa[4]	Y	Q	Q	L	P	G	T	A	P	K	L	L	I	Y	D	N	N	K	R
rel. oomcaa[5]	95%	93%	81%	74%	100%	93%	86%	95%	100%	83%	98%	95%	95%	95%	31%	67%	71%	43%	95%
pos occupied[6]	3	3	4	5	1	4	4	3	1	4	2	2	3	3	10	5	4	9	3

Table 5A: Analysis of V lambda subgroup 1

	CDR II																		
amino acid[1]	55	56	A	B	C	D	E	57	58	59	60	61	62	63	64	65	66	A	B
A	1														5				
B																			
C																			
D											38								
E																			
F													38						
G								41			2				36				
H											1								
I									17				3						
K																	38		
L		1								1									
M																			
N																			
P	38									38									
Q																			
R												42					4		
S	2	40								2				42		42			
T															1				
V									24				1						
W																			
X																			
Y																			
Z																			
-			41	41	41	41	42											42	42
unknown (?)																			
not sequenced	1	1						1	1	1	1								
sum of seq[2]	41	41	41	41	41	41	42	41	41	41	41	42	42	42	42	42	42	42	42
oomcaa[3]	38	40	41	41	41	41	42	41	24	38	38	42	38	42	36	42	38	42	42
mcaa[4]	P	S	-	-	-	-	-	G	V	P	D	R	F	S	G	S	K	-	-
rel. oomcaa[5]	93%	98%	100%	100%	100%	100%	100%	100%	59%	93%	93%	100%	90%	100%	86%	100%	90%	100%	100%
pos occupied[6]	3	2	1	1	1	1	1	1	2	3	3	1	3	1	3	1	2	1	1

Table 5A: Analysis of V lambda subgroup 1

	Framework III																		
amino acid[1]	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85
A		1	3		41			24						2				38	1
B																			
C																			
D		1													1	41			37
E													1		24		42		1
F																			
G		40						17		1	42				15				
H													1						2
I									41										1
K																			
L							42					41							
M																			
N																1			
P														2					
Q													31						
R													8						
S	42		1	42		24				20				20				1	
T			38			18				21				17				3	
V					1			1	1			1		1					
W													1		2				
X																			
Y																			
Z																			
-																			
unknown (?)																			
not sequenced																			
sum of seq[2]	42	42	42	42	42	42	42	42	42	42	42	42	42	42	42	42	42	42	42
oomcaa[3]	42	40	38	42	41	24	42	24	41	21	42	41	31	20	24	41	42	38	37
mcaa[4]	S	G	T	S	A	S	L	A	I	T	G	L	Q	S	E	D	E	A	D
rel. oomcaa[5]	100%	95%	90%	100%	98%	57%	100%	57%	98%	50%	100%	98%	74%	48%	57%	98%	100%	90%	88%
pos occupied[6]	1	3	3	1	2	2	1	3	2	3	1	2	5	5	4	2	1	3	5

Table 5A: Analysis of V lambda subgroup 1

				CDR III															
amino acid[1]	86	87	88	89	90	91	92	93	94	95	A	B	C	D	E	F	96	97	98
A				22	15			1				16					4	1	
B																			
C			42																
D							39	17			7								
E												1					1		
F		2								1									36
G				14				1				17	1				5	1	
H		1											1						
I											1							1	
K											1								
L				1						37			1					1	
M																		1	
N							2	2			9	1							
P										1							6		
Q				3															
R									5	1	2						2		
S					4			17	35		18		1				1		
T					22			1	1		1								
V				1				1		1		2					9	34	
W						38											7		
X																			
Y	42	39				3		1									3		
Z																			
-											2	4	35	39	38	38	1		
unknown (?)																			
not sequenced				1	1	1	1	1	1	1	1	1	3	3	3	3	3	3	4
sum of seq[2]	42	42	42	41	41	41	41	41	41	41	41	41	39	39	38	38	39	39	36
oomcaa[3]	42	39	42	22	22	38	39	17	35	37	18	17	35	39	38	38	9	34	36
mcaa[4]	Y	Y	C	A	T	W	D	D	S	L	S	G	-	-	-	-	V	V	F
rel. oomcaa[5]	100%	93%	100%	54%	54%	93%	95%	41%	85%	90%	44%	41%	90%	100%	100%	100%	23%	87%	100%
pos occupied[6]	1	3	1	5	3	2	2	8	3	5	8	6	5	1	1	1	10	6	1

Table 5A: Analysis of V lambda subgroup 1

amino acid[1]	Framework IV											
	99	100	101	102	103	104	105	106	A	107	108	sum
A												285
B												
C												84
D												224
E		1										81
F												87
G	36	31	36							26		559
H												25
I												188
K					30							141
L						25			34			344
M												5
N					1							176
P											1	296
Q					3				1		18	251
R					1					2		156
S		1								2		720
T		3		36	1		36					359
V						11		36	1			282
W										1		92
X												
Y												202
Z												16
-												524
unknown (?)												
not sequenced	4	6	6	6	6	6	6	6	6	10	22	141
sum of seq[2]	36	36	36	36	36	36	36	36	36	31	19	
oomcaa[3]	36	31	36	36	30	25	36	36	34	26	18	
mcaa[4]	G	G	G	T	K	L	T	V	L	G	Q	
rel. oomcaa[5]	100%	86%	100%	100%	83%	69%	100%	100%	94%	84%	95%	
pos occupied[6]	1	4	1	1	5	2	1	1	3	4	2	

Table 5B: Analysis of V lambda subgroup 2

	Framework I																		
amino acid[1]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
A			35					30			6		1	1					
B																			
C																			
D																1			
E																			
F																			
G													42			42			
H	2																1		
I			1																28
K																			
L				40											3				1
M																			
N																			
P							42	6							40				
Q	22		4			41											42		
R								6	1										
S		41							40			42		42				43	
T					42				1										
V		1	2								36								14
W																			
X																			
Y																			
Z	16																		
-										42									
unknown (?)						1													
not sequenced	3	1	1	3	1	1	1	1	1	1	1	1							
sum of seq[2]	40	42	42	40	42	42	42	42	42	42	42	42	43	43	43	43	43	43	43
oomcaa[3]	22	41	35	40	42	41	42	30	40	42	36	42	42	42	40	42	42	43	28
mcaa[4]	Q	S	A	L	T	Q	P	A	S	-	V	S	G	S	P	G	Q	S	I
rel. oomcaa[5]	55%	98%	83%	100%	100%	98%	100%	71%	95%	100%	86%	100%	98%	98%	93%	98%	98%	100%	65%
pos occupied[6]	3	2	4	1	1	1	1	3	3	1	2	1	2	2	2	2	2	1	3

Table 5B: Analysis of V lambda subgroup 2

					CDRI														
amino acid[1]	20	21	22	23	24	25	26	27	D	E	28	29	30	31	A	32	33	34	35
A					3		1						1			1			
B																			
C				42					1					1					
D										39		1	4		5				
E															1				
F		1											1			4			
G						43		1				39	26						
H								1							1	1			
I		41			1						6								
K															4				
L		1														4			
M																			
N								1	3	4		1	4	3	28				
P								1											
Q																			
R									1				2						
S			42		3		3	35	38				5	1	2	4	1	42	
T	43				36		39	3				1		1					
V											37						41		
W																			43
X																			
Y								1				1		37		29			
Z																			
-															1				
unknown (?)															1				
not sequenced			1	1													1	1	
sum of seq[2]	43	43	42	42	43	43	43	43	43	43	43	43	43	43	43	43	42	42	43
oomcaa[3]	43	41	42	42	36	43	39	35	38	39	37	39	26	37	28	29	41	42	43
mcaa[4]	T	I	S	C	T	G	T	S	S	D	V	G	G	Y	N	Y	V	S	W
rel. oomcaa[5]	100%	95%	100%	100%	84%	100%	91%	81%	88%	91%	86%	91%	60%	86%	65%	67%	98%	100%	100%
pos occupied[6]	1	3	1	1	4	1	3	7	4	2	2	5	7	5	7	6	2	1	1

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Table 5B: Analysis of V lambda subgroup 2

	Framework II																		
amino acid[1]	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54
A					1	4		40											
B																			
C																			
D				1		2									20	1	2	1	
E															20			2	
F	2													7		1			
G						36									2	2		1	
H			2	34														1	
I							1				1	9	43				1		
K							40			41							1	21	
L			1	1							38	6							
M												26					1		
N				2											1		8	12	
P					41				43										
Q		41	39							2									
R		1					1										2		43
S					1									2			21	3	
T							1										7		
V						1		3			4	2				39			
W																			
X																			
Y	41			5										34				2	
Z																			
-																			
unknown (?)		1	1																
not sequenced																			
sum of seq[2]	43	43	43	43	43	43	43	43	43	43	43	43	43	43	43	43	43	43	43
oomcaa[3]	41	41	39	34	41	36	40	40	43	41	38	26	43	34	20	39	21	21	43
mcaa[4]	Y	Q	Q	H	P	G	K	A	P	K	L	M	I	Y	D	V	S	K	R
rel. oomcaa[5]	95%	95%	91%	79%	95%	84%	93%	93%	100%	95%	88%	60%	100%	79%	47%	91%	49%	49%	100%
pos occupied[6]	2	2	3	5	3	4	4	2	1	2	3	4	1	3	4	4	8	8	1

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Table 5B: Analysis of V lambda subgroup 2

	CDR II																		
amino acid[1]	55	56	A	B	C	D	E	57	58	59	60	61	62	63	64	65	66	A	B
A															2				
B																			
C																1			
D											17								
E																			
F													42						
G								43	1						41				
H											2								
I									3										
K																	42		
L											1		1						
M																			
N											19								
P	43									15									
Q																			
R												43					1		
S		43								28	2			43		42			
T																			
V									39										
W																			
X																			
Y											2								
Z																			
-			43	43	43	43	43											43	43
unknown (?)																			
not sequenced																			
sum of seq[2]	43	43	43	43	43	43	43	43	43	43	43	43	43	43	43	43	43	43	43
oomcaa[3]	43	43	43	43	43	43	43	43	39	28	19	43	42	43	41	42	42	43	43
mcaa[4]	P	S	-	-	-	-	-	G	V	S	N	R	F	S	G	S	K	-	-
rel. oomcaa[5]	100%	100%	100%	100%	100%	100%	100%	100%	91%	65%	44%	100%	98%	100%	95%	98%	98%	100%	100%
pos occupied[6]	1	1	1	1	1	1	1	1	3	2	6	1	2	1	2	2	2	1	1

Table 5B: Analysis of V lambda subgroup 2

	Framework III																		
amino acid[1]	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85
A		3		1	43									36				43	
B																			
C																			
D		1	2												3	42			39
E											1				38		43		
F																			
G		39									42				1				
H																			2
I									35										
K			1																
L							43					43							
M																			
N			38												1	1			1
P														2					
Q													41						
R													2						
S	42			1		43				42									
T			1	41				43		1				2					
V									8					3					
W																			
X																			
Y																			
Z																			
-																			
unknown (?)			1																1
not sequenced	1																		
sum of seq[2]	42	43	43	43	43	43	43	43	43	43	43	43	43	43	43	43	43	43	43
oomcaa[3]	42	39	38	41	43	43	43	43	35	42	42	43	41	36	38	42	43	43	39
mcaa[4]	S	G	N	T	A	S	L	T	I	S	G	L	Q	A	E	D	E	A	D
rel. oomcaa[5]	100%	91%	88%	95%	100%	100%	100%	100%	81%	98%	98%	100%	95%	84%	88%	98%	100%	100%	91%
pos occupied[6]	1	3	4	3	1	1	1	1	2	2	2	1	2	4	4	2	1	1	3

Table 5B: Analysis of V lambda subgroup 2

				CDR III															
amino acid[1]	86	87	88	89	90	91	92	93	94	95	A	B	C	D	E	F	96	97	98
A				2	1		21		1								1	1	
B																			
C			43	11															
D								3	1	2							1		
E							1	1											
F		3				3				1		1					5		42
G							1	21	3	4							1		
H						1													
I							1	1		1	2						1	7	
K										3									
L												1	1				6	5	
M																	1	1	
N									5	7	5						1		
P								1				4							
Q										1	2								
R							2		3			1					5		
S		1		30	41			12	23	14	9						1		
T							16	4	4	3	21								
V							1										11	28	
W																	5		
X																			
Y	43	39				39			1	6							4		
Z																			
-										1	3	36	42	43	43	43			
unknown (?)									2										
not sequenced					1						1							1	1
sum of seq[2]	43	43	43	43	42	43	43	43	43	43	42	43	43	43	43	43	43	42	42
oomcaa[3]	43	39	43	30	41	39	21	21	23	14	21	36	42	43	43	43	11	28	42
mcaa[4]	Y	Y	C	S	S	Y	A	G	S	S	T	-	-	-	-	-	V	V	F
rel. oomcaa[5]	100%	91%	100%	70%	98%	91%	49%	49%	53%	33%	50%	84%	98%	100%	100%	100%	26%	67%	100%
pos occupied[6]	1	3	1	3	2	3	7	7	8	11	6	5	2	1	1	1	13	5	1

Table 5B: Analysis of V lambda subgroup 2

amino acid[1]	99	100	101	102	103	104	105	106	A	107	108	sum
	Framework IV											
A		1										280
B												
C												99
D												188
E												107
F												113
G	42	33	42							19		567
H												48
I							1					184
K					36							189
L						28			40			264
M												29
N					1							146
P												238
Q					1						14	250
R		1			2					4		121
S							1			2		831
T		7		41			40					398
V						14		42	1			327
W												48
X												
Y					1							285
Z												16
-												555
unknown (?)												8
not sequenced	1	1	1	2	2	1	1	1	2	15	28	80
sum of seq[2]	42	42	42	41	41	42	42	42	41	25	14	
oomcaa[3]	42	33	42	41	36	28	40	42	40	19	14	
mcaa[4]	G	G	G	T	K	L	T	V	L	G	Q	
rel. oomcaa[5]	100%	79%	100%	100%	88%	67%	95%	100%	98%	76%	100%	
pos occupied[6]	1	4	1	1	5	2	3	1	2	3	1	

Table 5C: Analysis of V lambda subgroup 3

	Framework I																		
amino acid[1]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
A					1		1	2	7					20	1				27
B																			
C																			
D			5				10												
E			20										1			1			
F	1	1										1			1				
G			1													37			
H																			
I																			
K																	2		
L				37							4		1		9				
M																			
N																			
P							26	35	1						27				1
Q	4		4			38											36		
R																			
S	13	14			1		1		28			37		18					
T					36			1										38	
V			8	1					2		34		36						10
W																			
X																			
Y		23																	
Z																			
-	20									38									
unknown (?)																			
not sequenced																			
sum of seq[2]	38	38	38	38	38	38	38	38	38	38	38	38	38	38	38	38	38	38	38
oomcaa[3]	20	23	20	37	36	38	26	35	28	38	34	37	36	20	27	37	36	38	27
mcaa[4]	-	Y	E	L	T	Q	P	P	S	-	V	S	V	A	P	G	Q	T	A
rel. oomcaa[5]	53%	61%	53%	97%	95%	100%	68%	92%	74%	100%	89%	97%	95%	53%	71%	97%	95%	100%	71%
pos occupied[6]	4	3	5	2	3	1	4	3	4	1	2	2	3	2	4	2	2	1	3

Table 5C: Analysis of V lambda subgroup 3

					CDRI														
amino acid[1]	20	21	22	23	24	25	26	27	D	E	28	29	30	31	A	32	33	34	35
A			1					5					1	1			21	3	
B																			
C				38														5	
D							30	1					10			3		1	
E							2	2				1	3	6					
F														1		2			
G					9	38		1				23	4						
H							1									2		9	
I		38									9			1					
K								7					2	13					
L											28								
M	1													1					
N			2				4	9			1		2			1		2	
P			1									3							
Q					10									4					
R	25							2				10	1				1		
S	9		1		19			10					11	2		8		14	
T	3		33					1				1	4						
V																1	15		
W																			38
X																			
Y							1							8		20	1	4	
Z																			
-									38	38					37				
unknown (?)																			
not sequenced															1	1			
sum of seq[2]	38	38	38	38	38	38	38	38	38	38	38	38	38	37	37	37	38	38	38
oomcaa[3]	25	38	33	38	19	38	30	10	38	38	28	23	11	13	37	20	21	14	38
mcaa[4]	R	I	T	C	S	G	D	S	-	-	L	G	S	K	-	Y	A	S	W
rel. oomcaa[5]	66%	100%	87%	100%	50%	100%	79%	26%	100%	100%	74%	61%	29%	35%	100%	54%	55%	37%	100%
pos occupied[6]	4	1	5	1	3	1	5	9	1	1	3	5	9	9	1	7	4	7	1

Table 5C: Analysis of V lambda subgroup 3

	Framework II																		
amino acid[1]	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54
A								23								1		1	
B																			
C																			
D															9	22	2	8	
E			1												5	3		3	
F	3													2			1		
G						36									9	2			
H							1							1	3			1	
I										1			28				1		
K				32											2	6	1	13	
L			2							6	33	1							
M											1		1						
N																1	19	9	
P					36		1		38										
Q		37	35	1			36								9			1	
R		1		4		2									1	1		1	38
S				1	2			14									10	1	
T																2	4		
V								1		31	4	37	9						
W																			
X																			
Y	35													35					
Z																			
-																			
unknown (?)																			
not sequenced																			
sum of seq[2]	38	38	38	38	38	38	38	38	38	38	38	38	38	38	38	38	38	38	38
oomcaa[3]	35	37	35	32	36	36	36	23	38	31	33	37	28	35	9	22	19	13	38
mcaa[4]	Y	Q	Q	K	P	G	Q	A	P	V	L	V	I	Y	D	D	N	K	R
rel. oomcaa[5]	92%	97%	92%	84%	95%	95%	95%	61%	100%	82%	87%	97%	74%	92%	24%	58%	50%	34%	100%
pos occupied[6]	2	2	3	4	2	2	3	3	1	3	3	2	3	3	7	8	7	9	1

Table 5C: Analysis of V lambda subgroup 3

	CDR II																		
amino acid[1]	55	56	A	B	C	D	E	57	58	59	60	61	62	63	64	65	66	A	B
A		1																	
B																			
C																			
D											9								
E											27								
F													38						
G								38							38				
H																			
I									37										
K																			
L																			
M																			
N																	21		
P	37	1								36									
Q																			
R												38							
S	1	36								1				38		38	12		
T																	5		
V																			
W																			
X																			
Y																			
Z																			
-			38	38	38	38	38											38	38
unknown (?)											1								
not sequenced									1	1	1								
sum of seq[2]	38	38	38	38	38	38	38	38	37	37	37	38	38	38	38	38	38	38	38
oomcaa[3]	37	36	38	38	38	38	38	38	37	36	27	38	38	38	38	38	21	38	38
mcaa[4]	P	S	-	-	-	-	-	G	I	P	E	R	F	S	G	S	N	-	-
rel. oomcaa[5]	97%	95%	100%	100%	100%	100%	100%	100%	100%	97%	73%	100%	100%	100%	100%	100%	55%	100%	100%
pos occupied[6]	2	3	1	1	1	1	1	1	1	2	2	1	1	1	1	1	3	1	1

Table 5C: Analysis of V lambda subgroup 3

	Framework III																		
amino acid[1]	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85
A				1	36	1		1				11	1	34				38	
B																			
C																			
D																38			37
E													10		14		38		1
F																			
G		37									28				10				
H			1																
I						1		1	37	1					1				
K			1																
L							38								2				
M															10				
N			28							1									
P																			
Q		1											25						
R										1	10		1						
S	37		2			11				23				1					
T	1		6	37		25		36		12		13		2					
V					2				1			14	1	1	1				
W																			
X																			
Y																			
Z																			
-																			
unknown (?)																			
not sequenced																			
sum of seq[2]	38	38	38	38	38	38	38	38	38	38	38	38	38	38	38	38	38	38	38
oomcaa[3]	37	37	28	37	36	25	38	36	37	23	28	14	25	34	14	38	38	38	37
mcaa[4]	S	G	N	T	A	T	L	T	I	S	G	V	Q	A	E	D	E	A	D
rel. oomcaa[5]	97%	97%	74%	97%	95%	66%	100%	95%	97%	61%	74%	37%	66%	89%	37%	100%	100%	100%	97%
pos occupied[6]	2	2	5	2	2	4	1	3	2	5	2	3	5	4	6	1	1	1	2

Table 5C: Analysis of V lambda subgroup 3

amino acid[1]	86	87	88	89	90	91	92	93	94	95	A	B	C	D	E	F	96	97	98
				CDR III															
A					13	3	2			1	2						4		
B																			
C			38																
D							32	1	1		6								
E				1								2					2		
F		2						2											35
G									3	14	3			1			3	1	
H												12	1						
I																		4	
K											1								
L				1				1		1		1	1				4	2	
M									1								1	1	
N				10			2	1	2		10	1							
P									1				3				1		
Q				25						1	1								
R						10		1	2			2							
S				1	14	1		28	26	13		1				1			
T						1		3		7	2								
V					11												18	28	
W						23											1		
X																			
Y	38	36					1		1		1	3	1				3		
Z																			
-											10	15	31	36	37	36		1	
unknown (?)																			
not sequenced							1	1	1	1	2	1	1	1	1	1	1	1	3
sum of seq[2]	38	38	38	38	38	38	37	37	37	37	36	37	37	37	37	37	37	37	35
oomcaa[3]	38	36	38	25	14	23	32	28	26	14	10	15	31	36	37	36	18	28	35
mcaa[4]	Y	Y	C	Q	S	W	D	S	S	G	N	-	-	-	-	-	V	V	F
rel. oomcaa[5]	100%	95%	100%	66%	37%	61%	86%	76%	70%	38%	28%	41%	84%	97%	100%	97%	49%	76%	100%
pos occupied[6]	1	2	1	5	3	5	4	7	8	6	9	8	5	2	1	2	9	6	1

Table 5C: Analysis of V lambda subgroup 3

amino acid[1]	Framework IV 99	100	101	102	103	104	105	106	A	107	108	sum
A												265
B												
C										1		82
D												225
E					2							145
F												90
G	35	31	35							24		461
H												32
I												160
K					30							110
L						28			33			233
M												17
N												126
P									1			249
Q											7	275
R					2							154
S										2		501
T		4		35			35					347
V						7		35				308
W												62
X												
Y												211
Z												
-												603
unknown (?)												1
not sequenced	3	3	3	3	4	3	3	3	4	11	28	89
sum of seq[2]	35	35	35	35	34	35	35	35	34	27	7	
oomcaa[3]	35	31	35	35	30	28	35	35	33	24	7	
mcaa[4]	G	G	G	T	K	L	T	V	L	G	Q	
rel. oomcaa[5]	100%	89%	100%	100%	88%	80%	100%	100%	97%	89%	100%	
pos occupied[6]	1	2	1	1	3	2	1	1	2	3	1	

Table 6A: Analysis of V heavy chain subgroup 1A

	Framework I																			
amino acid[1]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
A					1	14			60							24	1			
B																				
C																				
D																				
E	1				2	1		2		64										
F																				
G								58	1						64					
H			2																	
I		2																		
K		2										57	64						60	
L			2	59							3									
M		1																		
N												6								
P														63						
Q	53		56		2	45														
R												1							3	
S							60		3					1		40	63			
T																			1	
V	2	55		1	55						61							64		64
W																				
X																				
Y																				
Z	3																			
-																				
unknown (?)																				
not sequenced	11	10	10	10	10	10	10	10	6	6	6	6	6	6	6	6	6	6	6	6
sum of seq[2]	59	60	60	60	60	60	60	60	64	64	64	64	64	64	64	64	64	64	64	64
oomcaa[3]	53	55	56	59	55	45	60	58	60	64	61	57	64	63	64	40	63	64	60	64
mcaa[4]	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V
rel. oomcaa[5]	90%	92%	93%	98%	92%	75%	100%	97%	94%	100%	95%	89%	100%	98%	100%	63%	98%	100%	94%	100%
pos occupied[6]	4	4	3	2	4	3	1	2	3	1	2	3	1	2	1	2	2	1	3	1

Table 6A: Analysis of V heavy chain subgroup 1A

amino acid[1]	21	22	23	24	25	26	27	28	29	30	31	A	B	32	33	34	35	36	37	38
											CDRI									
A				62				1							41					
B																				
C		63																		
D							1													
E																				
F									69					3		3				
G				1		69	41		1						23					
H										1				1			1			
I								1								61	1		1	
K			63							1	1									
L															1	2				
M																4				
N										2	5						4			
P															1					
Q																				
R		1	1							1	1									70
S	63				68		1			40	60			2			60			
T	1			2				68		25	3				3		4			
V															1				69	
W																		70		
X																				
Y							27							64						
Z																				
-												70	70							
unknown (?)																				
not sequenced	6	6	6	5	2	1														
sum of seq[2]	64	64	64	65	68	69	70	70	70	70	70	70	70	70	70	70	70	70	70	70
oomcaa[3]	63	63	63	62	68	69	41	68	69	40	60	70	70	64	41	61	60	70	69	70
mcaa[4]	S	C	K	A	S	G	G	T	F	S	S	-	-	Y	A	I	S	W	V	R
rel. oomcaa[5]	98%	98%	98%	95%	100%	100%	59%	97%	99%	57%	86%	100%	100%	91%	59%	87%	86%	100%	99%	100%
pos occupied[6]	2	2	2	3	1	1	4	3	2	6	5	1	1	4	6	4	5	1	2	1

Table 6A: Analysis of V heavy chain subgroup 1A

	Framework II																			
amino acid[1]	39	40	41	42	43	44	45	46	47	48	49	50	51	52	A	B	C	53	54	55
A		70									1				5					
B																				
C																				
D								1												
E								69												
F													2					3	39	
G			1	68		69			1		69	39			1					68
H			1																	
I													65	38				34		
K																				
L				1			68			1		1						2	4	
M										67				2				4		
N														4				3	22	
P			68				1								44					
Q	69				69													1	1	1
R	1			1		1						4						1		
S					1				1	1				22					1	1
T													1	2	4			1	3	
V										1			2	2	16			1		
W							1		67			26								
X																				
Y									1									20		
Z																				
-																70	70			
unknown (?)																				
not sequenced																				
sum of seq[2]	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70
oomcaa[3]	69	70	68	68	69	69	68	69	67	67	69	39	65	38	44	70	70	34	39	68
mcaa[4]	Q	A	P	G	Q	G	L	E	W	M	G	G	I	I	P	-	-	I	F	G
rel. oomcaa[5]	99%	100%	97%	97%	99%	99%	97%	99%	96%	96%	99%	56%	93%	54%	63%	100%	100%	49%	56%	97%
pos occupied[6]	2	1	3	3	2	2	3	2	4	4	2	4	4	6	5	1	1	10	6	3

Table 6A: Analysis of V heavy chain subgroup 1A

	CDR II																			
amino acid[1]	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75
A	1	34			69											43				
B																				
C																				
D	15		1							2							70			
E									1									33		
F				1				48				3		4						
G	1						3			67										
H			1																	
I	4												1	44				1		
K	1		2	1			47		1		1							8		
L	1	1						22				2		1		3				
M														21						
N	9		59				18													
P	1	7																		
Q	1	1				70			64											
R	2						2		1		69							1		
S		1	2		1										5				70	
T	34	26	4						3				66		65	24		27		67
V										1		65	3							3
W																				
X																				
Y			1	68																
Z																				
-																				
unknown (?)																				
not sequenced																				
sum of seq[2]	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70
oomcaa[3]	34	34	59	68	69	70	47	48	64	67	69	65	66	44	65	43	70	33	70	67
mcaa[4]	T	A	N	Y	A	Q	K	F	Q	G	R	V	T	I	T	A	D	E	S	T
rel. oomcaa[5]	49%	49%	84%	97%	99%	100%	67%	69%	91%	96%	99%	93%	94%	63%	93%	61%	100%	47%	100%	96%
pos occupied[6]	11	6	7	3	2	1	4	2	5	3	2	3	3	4	2	3	1	5	1	2

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Table 6A: Analysis of V heavy chain subgroup 1A

	Framework III																			
amino acid[1]	76	77	78	79	80	81	82	A	B	C	83	84	85	86	87	88	89	90	91	92
A			64			1						3			1	70				
B																				
C																				70
D						2							26	70						
E						64							44							
F																	1	1	2	
G									1											
H				1				1												
I		1					3	1	1								2			
K											3									
L					3		63			70							2			
M					67										1		1			
N	4							1	16											
P																				
Q				1		3														
R	3							23	1		62									
S	62		1					41	49			67			1					
T	1	69	2					3	2		4				67					
V			3				4				1						64			
W																				
X																				
Y				68														69	68	
Z																				
-																				
unknown (?)																				
not sequenced																				
sum of seq[2]	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70
oomcaa[3]	62	69	64	68	67	64	63	41	49	70	62	67	44	70	67	70	64	69	68	70
mcaa[4]	S	T	A	Y	M	E	L	S	S	L	R	S	E	D	T	A	V	Y	Y	C
rel. oomcaa[5]	89%	99%	91%	97%	96%	91%	90%	59%	70%	100%	89%	96%	63%	100%	96%	100%	91%	99%	97%	100%
pos occupied[6]	4	2	4	3	2	4	3	6	6	1	4	2	2	1	4	1	5	2	2	1

Table 6A: Analysis of V heavy chain subgroup 1A

	CDR III																			
amino acid[1]	93	94	95	96	97	98	99	100	A	B	C	D	E	F	G	H	I	J	K	101
A	66	2	16		1	1	1	4	1	2	2	1	1		1	1	1	2		1
B																				
C					1	1	16	2		1	1	7	2	1						
D			16	5	3		3	5	4	3	4			1	1	14				59
E			9				2			1			1			1				
F					1	3		2		3	1	2		2	1				28	2
G		2	14	13	20	10	14	5	20	15	16	3	3	4	15	1	1	7		
H										1	1	1		1						
I				2	5	2	2		2	2	1	1			1					
K		5			2	1			1											
L		1	4	4	2	5	2	1	1		4	2		1			1		1	
M			1		2		1		1			1	1						10	
N				2	2	1	2	1	2	2	2	2			1	1	4			
P				20	3		1	3	2	2	2	4	2	1	4	1		1		1
Q				1			1		1	1	1									
R		55	1	5	7	8	1	4		2		1		16						
S		1	1	5	5	5	5	21	5	11	8	4	3		2	1		2		1
T	1	3	3	5	4	1	3	4	2	5	2		1			1	1			
V	3		3	2	4	3	3	3	4	2	2	2	1	2	1					
W				1	1	3	1	1			2		3				1	5	1	
X																				
Y		1		2	3	20	5	4	9	1	2	11	20	10	6	9	10	7	1	
Z																				
-				1	2	2	3	6	11	11	14	23	26	26	31	34	46	39	21	1
unknown (?)													1		1	1		2	3	
not sequenced			2	2	2	4	4	4	4	5	5	5	5	5	5	5	5	5	5	5
sum of seq[2]	70	70	68	68	68	66	66	66	66	65	65	65	65	65	65	65	65	65	65	65
oomcaa[3]	66	55	16	20	20	20	16	21	20	15	16	23	26	26	31	34	46	39	28	59
mcaa[4]	A	R	A	P	G	Y	C	S	G	-	-	-	-	-	-	-	-	-	F	D
rel. oomcaa[5]	94%	79%	24%	29%	29%	30%	24%	32%	30%	23%	25%	35%	40%	40%	48%	52%	71%	60%	43%	91%
pos occupied[6]	3	8	10	14	18	15	18	15	15	17	17	15	12	11	11	10	8	7	6	6

Table 6A: Analysis of V heavy chain subgroup 1A

	Framework IV												
amino acid[1]	102	103	104	105	106	107	108	109	110	111	112	113	sum
A													670
B													
C													165
D		1	1										308
E	1	1											297
F	2												226
G			58		59	1	1						928
H				1									14
I	3								4				286
K				3		1							325
L	3			1			40	1					386
M	1						3						189
N				1									176
P	5											1	238
Q				52									494
R				1									351
S											53	51	972
T						54	11	1	51		1		736
V	15		1				1	54		54		1	699
W		59		1									243
X													
Y	34		1										542
Z													3
-	1												578
unknown (?)													8
not sequenced	5	9	9	10	11	14	14	14	15	16	16	17	406
sum of seq[2]	65	61	61	60	59	56	56	56	55	54	54	53	
oomcaa[3]	34	59	58	52	59	54	40	54	51	54	53	51	
mcaa[4]	Y	W	G	Q	G	T	L	V	T	V	S	S	
rel. oomcaa[5]	52%	97%	95%	87%	100%	96%	71%	96%	93%	100%	98%	96%	
pos occupied[6]	9	3	4	7	1	3	5	3	2	1	2	3	

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Table 6B: Analysis of V heavy chain subgroup 1B

	Framework I																			
amino acid[1]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
A									32							34				
B																				
C																				
D																				
E		1			5	1				35										
F																				
G								27							35					
H			1											1						
I																				1
K		3	1									34	33						33	
L			3	26	1															
M				1	1															
N																				
P									1					33			1			
Q	21		20			26														
R	1											1	2							
S							27									1	34			
T									1					1					2	
V	3	21			20						35							35		34
W																				
X																				
Y																				
Z																				
-																				
unknown (?)																				
not sequenced	15	15	15	13	13	13	13	13	6	5	5	5	5	5	5	5	5	5	5	5
sum of seq[2]	25	25	25	27	27	27	27	27	34	35	35	35	35	35	35	35	35	35	35	35
oomcaa[3]	21	21	20	26	20	26	27	27	32	35	35	34	33	33	35	34	34	35	33	34
mcaa[4]	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	A	S	V	K	V
rel. oomcaa[5]	84%	84%	80%	96%	74%	96%	100%	100%	94%	100%	100%	97%	94%	94%	100%	97%	97%	100%	94%	97%
pos occupied[6]	3	3	4	2	4	2	1	1	3	1	1	2	2	3	1	2	2	1	2	2

Table 6B: Analysis of V heavy chain subgroup 1B

											CDRI									
amino acid[1]	21	22	23	24	25	26	27	28	29	30	31	A	B	32	33	34	35	36	37	38
A				30							2				6					
B																				
C		35																		
D											1				5		1			1
E			3								1									
F							2		39					2	2					
G				1		40				1	14				1					1
H														3	1		34			
I								1		1						9				
K			28																	
L									1		1					5			2	
M																23				
N							1			1	3					1	3			
P															1					
Q			2								1				1		1			1
R			2					2						1						37
S	35				40			5		2	15			2	1					
T				3				32		34					1					
V				1			1			1	1				2	2			38	
W																		40		
X																				
Y							36				1			32	19		1			
Z																				
-												40	40							
unknown (?)																				
not sequenced	5	5	5	5																
sum of seq[2]	35	35	35	35	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
oomcaa[3]	35	35	28	30	40	40	36	32	39	34	15	40	40	32	19	23	34	40	38	37
mcaa[4]	S	C	K	A	S	G	Y	T	F	T	S	-	-	Y	Y	M	H	W	V	R
rel. oomcaa[5]	100%	100%	80%	86%	100%	100%	90%	80%	98%	85%	38%	100%	100%	80%	48%	58%	85%	100%	95%	93%
pos occupied[6]	1	1	4	4	1	1	4	4	2	6	10	1	1	5	11	5	5	1	2	4

Table 6B: Analysis of V heavy chain subgroup 1B

	Framework II																			
amino acid[1]	39	40	41	42	43	44	45	46	47	48	49	50	51	52	A	B	C	53	54	55
A		39				1					1				7			1		
B																				
C																				
D														1					1	
E				1				39										1	1	
F							2						1					1		
G				39		28					39	1			1			9	1	39
H																		2		
I										3			34							
K					1														1	
L			1				37						1							
M										37		2	4							
N														35				20	12	1
P		1	34				1								31					
Q	39				39			1												
R	1					10						4						3	1	
S			1			1								2				1	20	
T			4											1					3	
V														1	1					
W									40			33								
X																				
Y																		2		
Z																				
-																40	40			
unknown (?)																				
not sequenced																				
sum of seq[2]	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
oomcaa[3]	39	39	34	39	39	28	37	39	40	37	39	33	34	35	31	40	40	20	20	39
mcaa[4]	Q	A	P	G	Q	G	L	E	W	M	G	W	I	N	P	-	-	N	S	G
rel. oomcaa[5]	98%	98%	85%	98%	98%	70%	93%	98%	100%	93%	98%	83%	85%	88%	78%	100%	100%	50%	50%	98%
pos occupied[6]	2	2	4	2	2	4	3	2	1	2	2	4	4	5	4	1	1	9	8	2

Table 6B: Analysis of V heavy chain subgroup 1B

	CDR II																			
amino acid[1]	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75
A	1	2			27	2				1		1				2				12
B																				
C																				
D	1									4							35			
E	2		2			1				1						1				
F				4				39						3						
G	15		6		1					34										
H			1	1													1			
I		1	1									1	1	13						22
K	2	2	8				36		1							1				
L						1		1						1						
M														23				1		1
N	17		18				1										4			
P																			3	
Q						36			37											
R			2				1		2		37					34		1		
S	1			2	11		1									1			37	
T		35	2		1		1						39		40	1		38		5
V	1											38								
W											3									
X																				
Y				33																
Z																				
-																				
unknown (?)																				
not sequenced																				
sum of seq[2]	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
oomcaa[3]	17	35	18	33	27	36	36	39	37	34	37	38	39	23	40	34	35	38	37	22
mcaa[4]	N	T	N	Y	A	Q	K	F	Q	G	R	V	T	M	T	R	D	T	S	I
rel. oomcaa[5]	43%	88%	45%	83%	68%	90%	90%	98%	93%	85%	93%	95%	98%	58%	100%	85%	88%	95%	93%	55%
pos occupied[6]	8	4	8	4	4	4	5	2	3	4	2	3	2	4	1	6	3	3	2	4

Table 6B: Analysis of V heavy chain subgroup 1B

	Framework III																			
amino acid[1]	76	77	78	79	80	81	82	A	B	C	83	84	85	86	87	88	89	90	91	92
A			35									1	2			40				
B																				
C																				37
D	1					4							19	40			1			
E						35							19							
F			1									2							2	1
G						1		1	2											
H																				
I		1															1			
K											1									
L					2		39			39							2			1
M					37		1										2			
N	7							1	2											
P												1							1	
Q																				
R	4							2	16		37									
S	27			1				35	20		1	36						1	1	
T	1	39						1			1				40					
V			4		1					1							33			
W																				
X																				
Y				39														38	35	
Z																				
-																				
unknown (?)																				
not sequenced																	1	1	1	1
sum of seq[2]	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	39	39	39	39
oomcaa[3]	27	39	35	39	37	35	39	35	20	39	37	36	19	40	40	40	33	38	35	37
mcaa[4]	S	T	A	Y	M	E	L	S	S	L	R	S	D	D	T	A	V	Y	Y	C
rel. oomcaa[5]	68%	98%	88%	98%	93%	88%	98%	88%	50%	98%	93%	90%	48%	100%	100%	100%	85%	97%	90%	95%
pos occupied[6]	5	2	3	2	3	3	2	5	4	2	4	4	3	1	1	1	5	2	4	3

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Table 6B: Analysis of V heavy chain subgroup 1B

	CDR III																			
amino acid[1]	93	94	95	96	97	98	99	100	A	B	C	D	E	F	G	H	I	J	K	101
A	37	1	6		1	1		2	3	1	3		1					5		
B																				
C		1				3				2	1									
D			7		5	2	3	1	5	4		1		2	2	1	2			27
E			2		1			1	1		2		1		1					
F				1	1	3			2	1	1	1	1					2	15	
G		1	7	7	5	5	9	4	7	1	3		2	2	1		1	3		1
H			1				2			1	1									
I		1		1	1	3	1	1	1	1	1	1							1	
K		1			1				1	1		1		1			1			
L			2	4	4	4	3			1	2	1	1	2		1			2	
M				2		1	1								1				4	
N					1			1		1	1	1			3		1			1
P				6	4				1	1		3	2				1			
Q					1							1	2	1						
R	1	31		5	1	1	3					1		1				1		
S		1	3	3	1	4	3	6	3	2	2	1		1						
T		2	1	1	2	2	1	5	1	1	1		1			1		1		
V	1		7	1	1		1	3	1	2		1			1	2	1			1
W			1		1		2	2		1	1					1		4		
X																				
Y				5	5	4	2	3		4	3	3	2	1	2	5	6	2		
Z																				
-				1	1	4	6	8	10	11	14	20	23	25	25	25	23	18	11	6
unknown (?)																			3	
not sequenced	1	1	3	3	3	3	3	3	4	4	4	4	4	4	4	4	4	4	4	4
sum of seq[2]	39	39	37	37	37	37	37	37	36	36	36	36	36	36	36	36	36	36	36	36
oomcaa[3]	37	31	7	7	5	5	9	8	10	11	14	20	23	25	25	25	23	18	15	27
mcaa[4]	A	R	D	G	D	G	G	-	-	-	-	-	-	-	-	-	-	-	F	D
rel. oomcaa[5]	95%	79%	19%	19%	14%	14%	24%	22%	28%	31%	39%	56%	64%	69%	69%	69%	64%	50%	42%	75%
pos occupied[6]	3	8	10	12	18	13	13	12	12	17	14	13	10	9	8	7	8	8	5	5

Table 6B: Analysis of V heavy chain subgroup 1B

amino acid[1]	Framework IV												sum
	102	103	104	105	106	107	108	109	110	111	112	113	
A													340
B													
C													79
D	2												179
E				1									159
F	1												130
G			27		26					1			450
H	1												51
I	7								3				113
K				2									194
L							12			1			204
M							2						144
N	1												138
P	1			1									128
Q				23									253
R							1						247
S	3								1		18	18	432
T						21	6		16		1		390
V	6							21		18			342
W		29											158
X													
Y	11												294
Z													
-	3												394
unknown (?)	·												3
not sequenced	4	11	13	13	14	19	19	19	20	20	21	22	458
sum of seq[2]	36	29	27	27	26	21	21	21	20	20	19	18	
oomcaa[3]	11	29	27	23	26	21	12	21	16	18	18	18	
mcaa[4]	Y	W	G	Q	G	T	L	V	T	V	S	S	
rel. oomcaa[5]	31%	100%	100%	85%	100%	100%	57%	100%	80%	90%	95%	100%	
pos occupied[6]	10	1	1	4	1	1	4	1	3	3	2	1	

Table 6C: Analysis of V heavy chain subgroup 2

	Framework I																			
amino acid[1]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
A										3										
B																				
C																				
D																				
E	1					6										2				
F																				
G								6												
H																				
I		1																		
K					3								6		1					
L				6							6							6		6
M																				
N							1													
P							1		6					6			1			
Q	2															4				
R					2															
S							4													
T			6		1					2					5		5		6	
V		5								1		6								
W																				
X																				
Y																				
Z	3																			
-																				
unknown (?)																				
not sequenced	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
sum of seq[2]	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
oomcaa[3]	3	5	6	6	3	6	4	6	6	3	6	6	6	6	5	4	5	6	6	6
mcaa[4]	Z	V	T	L	K	E	S	G	P	A	L	V	K	P	T	Q	T	L	T	L
rel. oomcaa[5]	50%	83%	100%	100%	50%	100%	67%	100%	100%	50%	100%	100%	100%	100%	83%	67%	83%	100%	100%	100%
pos occupied[6]	3	2	1	1	3	1	3	1	1	3	1	1	1	1	2	2	2	1	1	1

Table 6C: Analysis of V heavy chain subgroup 2

											CDRI									
amino acid[1]	21	22	23	24	25	26	27	28	29	30	31	A	B	32	33	34	35	36	37	38
A								1				1			1					
B																				
C		7													2					
D												1								
E																				
F				3			6		1											
G						7							4		3		3			
H																				
I													1						7	
K																				
L				2			1		6											
M														5						
N											2									
P																				
Q																				
R													2		1					7
S			1		6			6		6	2	4					4			
T	6		6							1	3	1								
V				2										2		7				
W																		7		
X																				
Y					1															
Z																				
-																				
unknown (?)																				
not sequenced	1																			
sum of seq[2]	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
oomcaa[3]	6	7	6	3	6	7	6	6	6	6	3	4	4	5	3	7	4	7	7	7
mcaa[4]	T	C	T	F	S	G	F	S	L	S	T	S	G	M	G	V	S	W	I	R
rel. oomcaa[5]	100%	100%	86%	43%	86%	100%	86%	86%	86%	86%	43%	57%	57%	71%	43%	100%	57%	100%	100%	100%
pos occupied[6]	1	1	2	3	2	1	2	2	2	2	3	4	3	2	4	1	2	1	1	1

Table 6C: Analysis of V heavy chain subgroup 2

	Framework II																			
amino acid[1]	39	40	41	42	43	44	45	46	47	48	49	50	51	52	A	B	C	53	54	55
A						6					7									
B																				
C																				
D														2					3	6
E								7												
F														2						
G		1		7		1														
H												2								1
I													6							
K					6															
L							7			7		2	1	1						
M																				
N																			3	
P		5	7																	
Q	6																			
R	1				1							2								
S		1																2		
T																				
V																				
W									7			1						4		
X														1				1	1	
Y														1	1					
Z																				
-															6	7	7			
unknown (?)																				
not sequenced																				
sum of seq[2]	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
oomcaa[3]	6	5	7	7	6	6	7	7	7	7	7	2	6	2	6	7	7	4	3	6
mcaa[4]	Q	P	P	G	K	A	L	E	W	L	A	H	I	D	-	-	-	W	D	D
rel. oomcaa[5]	86%	71%	100%	100%	86%	86%	100%	100%	100%	100%	100%	29%	86%	29%	86%	100%	100%	57%	43%	86%
pos occupied[6]	2	3	1	1	2	2	1	1	1	1	1	4	2	5	2	1	1	3	3	2

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Table 6C: Analysis of V heavy chain subgroup 2

	CDR II																			
amino acid[1]	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75
A																				
B																				
C																				
D	5																6	1		
E	1								1											
F		1		1																
G																				
H				1																
I														6						
K	1	6							4							6				6
L								7				7								
M																				
N																	1			
P						2														
Q																				
R			2			1			2		7					1				1
S			2		6		7			4			1		5				7	
T						4				3			6		2			6		
V														1						
W				1																
X					1															
Y			3	4																
Z																				
-																				
unknown (?)																				
not sequenced																				
sum of seq[2]	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
oomcaa[3]	5	6	3	4	6	4	7	7	4	4	7	7	6	6	5	6	6	6	7	6
mcaa[4]	D	K	Y	Y	S	T	S	L	K	S	R	L	T	I	S	K	D	T	S	K
rel. oomcaa[5]	71%	86%	43%	57%	86%	57%	100%	100%	57%	57%	100%	100%	86%	86%	71%	86%	86%	86%	100%	86%
pos occupied[6]	3	2	3	4	2	3	1	1	3	2	1	1	2	2	2	2	2	2	1	2

Table 6C: Analysis of V heavy chain subgroup 2

	Framework III																			
amino acid[1]	76	77	78	79	80	81	82	A	B	C	83	84	85	86	87	88	89	90	91	92
A													1			5				
B																				
C																				7
D											6			7						
E																				
F					1															
G																2				
H																				
I						2		1												
K																				
L					6															
M							7			5										
N	5								6		1									
P												7								
Q		7																		
R																				
S	2																			
T						5		5							7		7			
V			7	7						1			6							
W																				
X																				
Y																		7	7	
Z																				
-								1	1	1										
unknown (?)																				
not sequenced																				
sum of seq[2]	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
oomcaa[3]	5	7	7	7	6	5	7	5	6	5	6	7	6	7	7	5	7	7	7	7
mcaa[4]	N	Q	V	V	L	T	M	T	N	M	D	P	V	D	T	A	T	Y	Y	C
rel. oomcaa[5]	71%	100%	100%	100%	86%	71%	100%	71%	86%	71%	86%	100%	86%	100%	100%	71%	100%	100%	100%	100%
pos occupied[6]	2	1	1	1	2	2	1	3	2	3	2	1	2	1	1	2	1	1	1	1

Table 6C: Analysis of V heavy chain subgroup 2

	CDR III																			
amino acid[1]	93	94	95	96	97	98	99	100	A	B	C	D	E	F	G	H	I	J	K	101
A	5							1	2	1										
B																				
C																				
D																				6
E								2			1									
F																			3	
G						1	1		1	2	1	1	1	1						
H		1		1																
I			3			2														
K							1													
L								1		1									1	
M								1											2	
N				1	2												1			
P				1	1		1		1											
Q			1																	
R		6	1			1			1											
S				1		1	1													
T				1			1		1											
V	2		1	1	1		1	1			1									
W						1									1			1		
X																				
Y					2						1	2	1	1	1			2		
Z																				
-										2	2	3	4	4	4	6	5	3		
unknown (?)																				
not sequenced			1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
sum of seq[2]	7	7	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
oomcaa[3]	5	6	3	1	2	2	1	2	2	2	2	3	4	4	4	6	5	3	3	6
mcaa[4]	A	R	I	H	N	I	G	E	A	-	-	-	-	-	-	-	-	-	F	D
rel. oomcaa[5]	71%	86%	50%	17%	33%	33%	17%	33%	33%	33%	33%	50%	67%	67%	67%	100%	83%	50%	50%	100%
pos occupied[6]	2	2	4	6	4	5	6	5	5	4	5	3	3	3	3	1	2	3	3	1

Table 6C: Analysis of V heavy chain subgroup 2

amino acid[1]	Framework IV 102	103	104	105	106	107	108	109	110	111	112	113	sum
A									1				35
B													
C													16
D													43
E													21
F													18
G			6		6								55
H													6
I													29
K				1			1						42
L	1						3						78
M													20
N													23
P	1						1						41
Q				3									23
R				2									41
S											6	3	82
T						6	1		5				102
V	3							6		6			68
W		6											29
X													4
Y	1												35
Z													3
-													56
unknown (?)													
not sequenced	1	1	1	1	1	1	1	1	1	1	1	4	54
sum of seq[2]	6	6	6	6	6	6	6	6	6	6	6	3	
oomcaa[3]	3	6	6	3	6	6	3	6	5	6	6	3	
mcaa[4]	V	W	G	Q	G	T	L	V	T	V	S	S	
rel. oomcaa[5]	50%	100%	100%	50%	100%	100%	50%	100%	83%	100%	100%	100%	
pos occupied[6]	4	1	1	3	1	1	4	1	2	1	1	1	

Table 6D: Analysis of V heavy chain subgroup 3

	Frame														
amino acid[1]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
A					1		1			12		1		3	1
B			1			1							1		
C															
D	1					1				16					
E	110		9		15	166			9				8		2
F											4				
G								181	193	174		1			202
H			5										4		
I												9			
K		5	3										26		
L		1	5	176	43						140			1	
M		12		1											
N										1					
P													1	194	
Q	41		138	1	3	12							162		
R			6										4		
S							178			2				8	
T							1								
V	5	147		1	118						62	195			
W															1
X															
Y															
Z	8														
-															
unknown (?)															
not sequenced	47	47	45	33	32	32	32	31	10	7	6	6	6	6	6
sum of seq[2]	165	165	167	179	180	180	180	181	202	205	206	206	206	206	206
oomcaa[3]	110	147	138	176	118	166	178	181	193	174	140	195	162	194	202
mcaa[4]	E	V	Q	L	V	E	S	G	G	G	L	V	Q	P	G
rel. oomcaa[5]	67%	89%	83%	98%	66%	92%	99%	100%	96%	85%	68%	95%	79%	94%	98%
pos occupied[6]	5	4	7	4	5	4	3	1	2	5	3	4	7	4	4

Table 6D: Analysis of V heavy chain subgroup 3

	work I														
amino acid[1]	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
A								183	192		1				
B															
C						1	209								
D															7
E	8							8			3		1		
F		1	1			1						201		201	
G	134								2		207				3
H															1
I								2				3	17	1	
K				15											4
L			205		201							6		3	
M			1										1		
N													10		10
P								1					2		
Q			1												
R	62			191											11
S		206				207		4	2	209			15		174
T	4	1		2				4	4			1	163		
V					8			7	9				1	6	
W															
X															
Y															
Z															
-															
unknown (?)															
not sequenced	4	4	4	4	3	3	3	3	3	3	1	1	2	1	2
sum of seq[2]	208	208	208	208	209	209	209	209	209	209	211	211	210	211	210
oomcaa[3]	134	206	205	191	201	207	209	183	192	209	207	201	163	201	174
mcaa[4]	G	S	L	R	L	S	C	A	A	S	G	F	T	F	S
rel. oomcaa[5]	64%	99%	99%	92%	96%	99%	100%	88%	92%	100%	98%	95%	78%	95%	83%
pos occupied[6]	4	3	4	3	2	3	1	7	5	1	3	4	8	4	7

Table 6D: Analysis of V heavy chain subgroup 3

	CDRI								Framew						
amino acid[1]	31	A	B	32	33	34	35	36	37	38	39	40	41	42	43
A	1			17	80		1			1		187		1	
B															
C												1		1	
D	26			3	7		2								
E	1				10									1	1
F				5											
G	13				31		1					2		209	
H				4			88								
I	1			1		15			12						
K	7										1				202
L	3					3			2	3	1	2	1		
M						193									
N	35			8	3		34								
P				1			1					4	191		
Q											209		1		1
R	7									207		7			8
S	103			17	8		72					3	14		
T	9				15		10					4	5		
V	2				7	1			197			2			
W					30			212							
X	1														
Y	1			154	19		3								
Z															
-		210	210												
unknown (?)															
not sequenced	2			2	2				1	1	1				
sum of seq[2]	210	210	210	210	210	212	212	212	211	211	211	212	212	212	212
oomcaa[3]	103	210	210	154	80	193	88	212	197	207	209	187	191	209	202
mcaa[4]	S	-	-	Y	A	M	H	W	V	R	Q	A	P	G	K
rel. oomcaa[5]	49%	100%	100%	73%	38%	91%	42%	100%	93%	98%	99%	88%	90%	99%	95%
pos occupied[6]	14	1	1	9	10	4	9	1	3	3	3	9	5	4	4

Table 6D: Analysis of V heavy chain subgroup 3

	work II														
amino acid[1]	44	45	46	47	48	49	50	51	52	A	B	C	53	54	55
A	1					77	42		1	2		14		7	
B			3							1					
C													1		
D			1							7			94	8	3
E			198						3	2	1		2		1
F							7	1	2	1				1	8
G	207					33	11		10	46			4	163	85
H							6			1					
I					3		3	191		1					1
K								1	37	2	30		3	1	
L		211			5		12	1							
M							1	1							
N							13		7	9	2		13	11	1
P		1								1			1		
Q			7				7			10					
R	1						24	1	17	5	1		2		16
S	3			1		102	11	9	118	43		1	74	17	82
T							3	5	4	2		13	12	3	3
V			3		204		49	2		1		6			
W				210			1		8	6					
X													4		3
Y				1			22		5	58					8
Z															
-										14	178	178	2	1	1
unknown (?)															
not sequenced															
sum of seq[2]	212	212	212	212	212	212	212	212	212	212	212	212	212	212	212
oomcaa[3]	207	211	198	210	204	102	49	191	118	58	178	178	94	163	85
mcaa[4]	G	L	E	W	V	S	V	I	S	Y	-	-	D	G	G
rel. oomcaa[5]	98%	100%	93%	99%	96%	48%	23%	90%	56%	27%	84%	84%	44%	77%	40%
pos occupied[6]	4	2	5	3	3	3	15	9	11	19	5	5	12	9	12

Table 6D: Analysis of V heavy chain subgroup 3

amino acid[1]	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70
	CDR II														
A	9	1	2		174	33							1		
B	1	2													
C															
D	11		17			160									
E	8	3	2			1			2						
F	1		3	2								207			
G	5	1	5		4	5				212	1				
H	1		4												
I	3	37	2					8					14	208	
K	1	61							199		8				
L	1	1	1		1							1		1	
M	8		2		1										
N	51		4			2			2						
P	1	1			6	8	18		1						
Q	3	2							2		2				
R	5	4			5				6		201				
S	48		11		4		193					2	7		211
T	42	97	5		7								189		1
V		2			10	2		204				1		3	
W			2												
X	4		1			1									
Y	9		151	210			1					1	1		
Z															
-															
unknown (?)															
not sequenced															
sum of seq[2]	212	212	212	212	212	212	212	212	212	212	212	212	212	212	212
oomcaa[3]	51	97	151	210	174	160	193	204	199	212	201	207	189	208	211
mcaa[4]	N	T	Y	Y	A	D	S	V	K	G	R	F	T	I	S
rel. oomcaa[5]	24%	46%	71%	99%	82%	75%	91%	96%	94%	100%	95%	98%	89%	98%	100%
pos occupied[6]	19	12	15	2	9	8	3	2	6	1	4	5	5	3	2

Table 6D: Analysis of V heavy chain subgroup 3

	Framework III														
amino acid[1]	71	72	73	74	75	76	77	78	79	80	81	82	A	B	C
A				57			1	8						1	
B											2				
C															
D		199	38		2	2			1				10		
E		6			4						5				
F									13						
G													1	4	
H						1			1		2		2		
I			1				2	2				3	1	1	
K					186	6							3		
L								188		209		3	1		212
M	1				2		10	3		2		205			
N		5	170		2	188					3		181	10	
P							1								
Q					7						199				
R	211				1	1							2	8	
S				153	8	10	56		3				6	186	
T							142				1		4	2	
V				1				11		1		1			
W															
X		2	2			4							1		
Y									194						
Z															
-															
unknown (?)															
not sequenced			1	1											
sum of seq[2]	212	212	211	211	212	212	212	212	212	212	212	212	212	212	212
oomcaa[3]	211	199	170	153	186	188	142	188	194	209	199	205	181	186	212
mcaa[4]	R	D	N	S	K	N	T	L	Y	L	Q	M	N	S	L
rel. oomcaa[5]	100%	94%	81%	73%	88%	89%	67%	89%	92%	99%	94%	97%	85%	88%	100%
pos occupied[6]	2	4	4	3	8	7	6	5	5	3	6	4	11	7	1

Table 6D: Analysis of V heavy chain subgroup 3

amino acid[1]	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97
A		149	1		1	207					173	2	15	9	11
B															
C									1	210		5	2		1
D		5	15	209								2	54	7	6
E	1		190										11	2	11
F							1		15			1		9	6
G	1	1	6			4	1				2	8	34	26	35
H		1							1					3	11
I		8					2						4	15	10
K	30											60	4	3	5
L							18					1	6	11	7
M					2		1							6	1
N		1		1								2	20	4	3
P		9									1	3	4	29	10
Q				1								5	3	9	2
R	177											103	9	30	19
S		1			1							3	9	8	11
T	3	28			207		1				25	15	7	6	20
V		9					187				10	1	7	7	15
W										1			3	4	3
X				1											
Y								211	194				12	9	8
Z															
-													1	3	4
unknown (?)															
not sequenced					1	1	1	1	1	1	1	1	7	12	13
sum of seq[7]	212	212	212	212	211	211	211	211	211	211	211	211	205	200	199
oomcaa[3]	177	149	190	209	207	207	187	211	194	210	173	103	54	30	35
mcaa[4]	R	A	E	D	T	A	V	Y	Y	C	A	R	D	R	G
rel. oomcaa[5]	83%	70%	90%	99%	98%	98%	89%	100%	92%	100%	82%	49%	26%	15%	18%
pos occupied[6]	5	10	4	4	4	2	7	1	4	2	5	14	18	20	21

Table 6D: Analysis of V heavy chain subgroup 3

	CDR III														
amino acid[1]	98	99	100	A	B	C	D	E	F	G	H	I	J	K	101
A	7	13	7	9	6	2	3	5	5		9		13		2
B															
C	13	5		1	2	11	3		2					1	
D	11	7	10	4	2	3	10	3	3	1		3	2		146
E	6	3	1	13		1	1								1
F	3	5	4	5	5	6	3	5	7	2		1	1	65	1
G	34	17	35	17	14	23	10	5	1	5	3	2	32		6
H	3	4	3	2	9	2		1	3	1	2	8	1		
I	6	11	4	4	3	1	3	10	3	3	2		1	2	
K	2	11			3	1									
L	26	13	4	12	8	2	6	3	10	3				2	1
M		1	2								1			32	
N	4	6	4	3	2	2	6				2	5			2
P	6	5	5	6	9	8	2	3	2	1		3		9	
Q	4		1	1	1	1	1					1			
R	4	10	9	7	5	5	2	3	1		1		2		4
S	16	28	27	25	24	8	11	9	3		2	3	1	1	1
T	6	12	9	17	17	1	2	5	1	9	3	1			
V	13	7	15	4	3	6	2	12		1	1	1	1		
W	6	5	6	7	2	4				1		6	10		
X				1											1
Y	16	14	17	5	8	18	20	13	20	25	28	32	28		
Z															
-	12	21	35	54	73	87	102	110	126	135	134	120	91	71	21
unknown (?)							3	2	1	1			3	2	
not sequenced	14	14	14	14	15	19	21	22	23	23	23	25	25	26	25
sum of seq[2]	198	198	198	197	196	192	190	189	188	188	188	186	186	185	186
oomcaa[3]	34	28	35	54	73	87	102	110	126	135	134	120	91	71	146
mcaa[4]	G	S	G	-	-	-	-	-	-	-	-	-	-	-	D
rel. oomcaa[5]	17%	14%	18%	27%	37%	45%	54%	58%	67%	72%	71%	65%	49%	38%	78%
pos occupied[6]	20	20	19	20	19	20	17	14	14	12	12	13	12	8	11

Table 6D: Analysis of V heavy chain subgroup 3

amino acid[1]	102	103	104	105	106	107	108	109	110	111	112	113	sum
	Framework IV												
A	1		1			2							1767
B				1									13
C													470
D	2												1121
E					1								832
F	2												807
G			140		130		1						2743
H	4												179
I	15								1	1			651
K				13									933
L	10			1			91					2	1881
M							6						496
N	1					1							844
P	17					1	1						568
Q				111									949
R				8									1413
S	7	1									118	110	3009
T						123	27		122			1	1426
V	34		1			1		125		119			1851
W		158											686
X													26
Y	82												1598
Z													8
-	9	2	2	2	2	2	2	2	2	2	1	1	2023
unknown (?)													12
not sequenced	27	50	67	75	78	81	83	84	86	89	92	97	1650
sum of seq[2]	184	161	144	136	133	130	128	127	125	122	119	114	
oomcaa[3]	82	158	140	111	130	123	91	125	122	119	118	110	
mcaa[4]	Y	W	G	Q	G	T	L	V	T	V	S	S	
rel. oomcaa[5]	45%	98%	97%	82%	98%	95%	71%	98%	98%	98%	99%	96%	
pos occupied[6]	12	3	4	6	3	6	6	2	3	3	2	4	

Table 6E: Analysis of V heavy chain subgroup 4

	Framework I																			
amino acid[1]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
A									19					1			1		1	
B																				
C																				
D																				
E						32										44				
F																				
G								54	1	53						2				
H			4		2															
I																				
K												1	54						1	
L		7		54							53	19		1				53		50
M																				
N																				
P									33					51	1					2
Q	52		50		51	20										7				
R	1																			
S							33								52				52	
T									1								52			
V		47				1						34								1
W							20													
X																				
Y																				
Z	1																			
-																				
unknown (?)																				
not sequenced	3	3	3	3	4	4	4	3	3	4	4	3	3	4	4	4	4	4	3	4
sum of seq[2]	54	54	54	54	53	53	53	54	54	53	53	54	54	53	53	53	53	53	54	53
oomcaa[3]	52	47	50	54	51	32	33	54	33	53	53	34	54	51	52	44	52	53	52	50
mcaa[4]	Q	V	Q	L	Q	E	S	G	P	G	L	V	K	P	S	E	T	L	S	L
rel. oomcaa[5]	96%	87%	93%	100%	96%	60%	62%	100%	61%	100%	100%	63%	100%	96%	98%	83%	98%	100%	96%	94%
pos occupied[6]	3	2	2	1	2	3	2	1	4	1	1	3	1	3	2	3	2	1	3	3

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Table 6E: Analysis of V heavy chain subgroup 4

											CDRI									
amino acid[1]	21	22	23	24	25	26	27	28	29	30	31	A	B	32	33	34	35	36	37	38
A			22											1						
B																				
C		53													1					
D			1								4	1	1	1			1			
E																				
F					1				22					1	1				1	
G						53	53				21	3	4				8			
H							1							2						
I			1					1	32										51	
K																				
L																			1	
M																				
N										1	1		2	2			1			
P								3												
Q											1									
R						1				3	2		1							57
S			2		35			51	1	52	25	5	9	1			44		1	
T	53		29								2	1					3			
V				55		1			1										3	
W												1			2	56		57		
X																				
Y					19		1							48	52					
Z																				
-												45	39							
unknown (?)																				
not sequenced	4	4	2	2	2	2	2	2	1	1	1			1	1	1				
sum of seq[2]	53	53	55	55	55	55	55	55	56	56	56	56	56	56	56	56	57	57	57	57
oomcaa[3]	53	53	29	55	35	53	53	51	32	52	25	45	39	48	52	56	44	57	51	57
mcaa[4]	T	C	T	V	S	G	G	S	I	S	S	-	-	Y	Y	W	S	W	I	R
rel. oomcaa[5]	100%	100%	53%	100%	64%	96%	96%	93%	57%	93%	45%	80%	70%	86%	93%	100%	77%	100%	89%	100%
pos occupied[6]	1	1	5	1	3	3	3	3	4	3	7	6	6	7	4	1	5	1	5	1

Table 6E: Analysis of V heavy chain subgroup 4

	Framework II																			
amino acid[1]	39	40	41	42	43	44	45	46	47	48	49	50	51	52	A	B	C	53	54	55
A			8	1							1									
B																				
C																				
D														1				1		
E				1				56				22								
F												1		1						
G				55		55					56	1						1		57
H		2																24		
I										54		1	54							
K					54															
L		1					55			2										
M																				
N														21						
P		50	49				2													
Q	56							1				1								
R					3	2						9		1						
S		3										7		1					52	
T	1	1																8	5	
V										1			3							
W									56											
X																				
Y									1			15		32				23		
Z																				
-															57	57	57			
unknown (?)																				
not sequenced																				
sum of seq[7]	57	57	57	57	57	57	57	57	57	57	57	57	57	57	57	57	57	57	57	57
oomcaa[1]	56	50	49	55	54	55	55	56	56	54	56	22	54	32	57	57	57	24	52	57
mcaa[4]	Q	P	P	G	K	G	L	E	W	I	G	E	I	Y	-	-	-	H	S	G
rel. oomcaa[5]	98%	88%	86%	96%	95%	96%	96%	98%	98%	95%	98%	39%	95%	56%	100%	100%	100%	42%	91%	100%
pos occupied[6]	2	5	2	3	2	2	2	2	2	3	2	8	2	6	1	1	1	5	2	1

Table 6E: Analysis of V heavy chain subgroup 4

	CDR II																			
amino acid[1]	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75
A		1									1		1			1				1
B																				
C																				
D			2									1					55			
E																	1			
F				3														1		
G	1									1										
H			2																	
I	1	1										1	1	48		3				
K					1				53									1		51
L						1		55				1				3				1
M														7				2		
N	2		40		53								2							1
P						54		1												
Q																	1			
R	2								3		56									2
S	49		1		2		56			56			1		56			1	57	
T	1	54	1			1			1				51		1			52		
V	1	1										53		2		50				1
W																				
X																				
Y			11	54																
Z																				
-																				
unknown (?)																				
not sequenced					1	1	1	1				1	1							
sum of seq[2]	57	57	57	57	56	56	56	56	57	57	57	56	56	57	57	57	57	57	57	57
oomcaa[3]	49	54	40	54	53	54	56	55	53	56	56	53	51	48	56	50	55	52	57	51
mcaa[4]	S	T	N	Y	N	P	S	L	K	S	R	V	T	I	S	V	D	T	S	K
rel. oomcaa[5]	86%	95%	70%	95%	95%	96%	100%	98%	93%	98%	98%	95%	91%	84%	98%	88%	96%	91%	100%	89%
pos occupied[6]	7	4	6	2	3	3	1	2	3	2	2	4	5	3	2	4	3	5	1	6

Table 6E: Analysis of V heavy chain subgroup 4

	Framework III																			
amino acid[1]	76	77	78	79	80	81	82	A	B	C	83	84	85	86	87	88	89	90	91	92
A												55	57			57				
B																				
C																				57
D					1									57						
E						1														
F			54						1											
G								1												
H																				
I			1					1			3									
K	3					46		2												
L		3	1		55		53			2							1			
M						1	1			1							1			
N	54					3		3	1											
P																				
Q		54			1	1														
R						2		2				1								
S			1	57		2	1	44	55		1				2				1	
T						1		4			53				55					
V							2			54		1					55			
W																				
X																				
Y																		57	56	
Z																				
-																				
unknown (?)																				
not sequenced																				
sum of seq[2]	57	57	57	57	57	57	57	57	57	57	57	57	57	57	57	57	57	57	57	57
oomcaa[3]	54	54	54	57	55	46	53	44	55	54	53	55	57	57	55	57	55	57	56	57
mcaa[4]	N	Q	F	S	L	K	L	S	S	V	T	A	A	D	T	A	V	Y	Y	C
rel. oomcaa[5]	95%	95%	95%	100%	96%	81%	93%	77%	96%	95%	93%	96%	100%	100%	96%	100%	96%	100%	98%	100%
pos occupied[6]	2	2	4	1	3	8	4	7	3	3	3	3	1	1	2	1	3	1	2	1

Table 6E: Analysis of V heavy chain subgroup 4

	CDR III																			
amino acid[1]	93	94	95	96	97	98	99	100	A	B	C	D	E	F	G	H	I	J	K	101
A	56		3	3	3	2	5	4	2	2	4		2	1		1	1	12		
B																				
C					1				1											
D			6		5	5	5	4	3	2	4	3	1		1	2	1			41
E			6	1	1	2	1			1	3	1	2	1						
F				4	1	1		2	3	2	2		1	1					31	
G			25	9	10	8	10	11	4	7	7	6	1	1	1	2	1	9		
H			1				1						1			1				2
I				1		2	4	1	3	2	3		1						1	
K			2	1						2	2			1						
L			2	6	7	3	5	3	2	4	1	5	3	3		1				
M				1	4		3	1		2	1								9	
N				3					2	1	1	5	1	1			2			
P				4	5	3	1	1	2	1	1	1	2	3	1	2	1			
Q					1	1		1			1	1			3					1
R		54	4	12	2	5	5	3	2	3	1	2			2	1				
S		1	1	4	8	8	1	2	5	7	4	2	1	1	1					
T		1	1	2	1	3	4	4	3	3			1	1	1					
V	1	1	4	2	2	5	4	4	7	3	1	2	1							
W			1	2	1	2	2	4	5	1	1	2		2	1		3	2		
X																				
Y				1	4	5	3	6	4	2	3	4	8	4	8	3	5	8		2
Z																				
-						1	2	4	6	9	11	16	23	27	29	34	31	14	4	
unknown (?)														1			1	1	1	
not sequenced			1	1	1	1	1	2	3	3	6	7	8	9	9	10	11	11	11	11
sum of seq[2]	57	57	56	56	56	56	56	55	54	54	51	50	49	48	48	47	46	46	46	46
oomcaa[3]	56	54	25	12	10	8	10	11	7	9	11	16	23	27	29	34	31	14	31	41
mcaa[4]	A	R	G	R	G	G	G	G	V	-	-	-	-	-	-	-	-	-	F	D
rel. oomcaa[5]	98%	95%	45%	21%	18%	14%	18%	20%	13%	17%	22%	32%	47%	56%	60%	72%	67%	30%	67%	89%
pos occupied[6]	2	4	12	16	16	16	16	16	16	18	18	13	15	13	10	9	8	5	4	4

Table 6E: Analysis of V heavy chain subgroup 4

	Framework IV												
amino acid[1]	102	103	104	105	106	107	108	109	110	111	112	113	sum
A						1			1				332
B													
C													113
D													210
E													176
F													135
G			41		40	1							674
H	1								1				45
I	9					1							282
K				3									278
L	4						19						540
M							9						43
N						1							204
P	3			2								2	281
Q				29									334
R	1			4			1						250
S	1			1							36	33	986
T				1		33	8		34				532
V	12							36		36			488
W		46											267
X													
Y	16												455
Z													1
-													466
unknown (?)													4
not sequenced	10	11	16	17	17	20	20	21	21	21	21	22	426
sum of seq[2]	47	46	41	40	40	37	37	36	36	36	36	35	
oomcaa[3]	16	46	41	29	40	33	19	36	34	36	36	33	
mcaa[4]	Y	W	G	Q	G	T	L	V	T	V	S	S	
rel. oomcaa[5]	34%	100%	100%	73%	100%	89%	51%	100%	94%	100%	100%	94%	
pos occupied[6]	8	1	1	6	1	5	4	1	3	1	1	2	

Table 6F: Analysis of V heavy chain subgroup 5

	Framework I																			
amino acid[1]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
A					1			1	89		1			1						
B																				
C							1													
D										2										
E	88	1			2				4	93						92				
F																	1			
G	1							92							94					
H																				
I																				96
K												94	94						77	
L		1		91		2												95		
M											3								1	
N																				
P				1					1					94						
Q	3		92		1	90										3			1	
R						1						1	1		1				17	
S							92										94			
T																				
V		90			89				1		91									
W																				
X																				
Y																				
Z																				
-																				
unknown (?)																				
not sequenced	5	5	5	5	4	4	4	4	2	2	2	2	2	2	2	2	2	2	1	1
sum of seq[2]	92	92	92	92	93	93	93	93	95	95	95	95	95	95	95	95	95	95	96	96
oomcaa[3]	88	90	92	91	89	90	92	92	89	93	91	94	94	94	94	92	94	95	77	96
mcaa[4]	E	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	E	S	L	K	I
rel. oomcaa[5]	96%	98%	100%	99%	96%	97%	99%	99%	94%	98%	96%	99%	99%	99%	99%	97%	99%	100%	80%	100%
pos occupied[6]	3	3	1	2	4	3	2	2	4	2	3	2	2	2	2	2	2	1	4	1

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Table 6F: Analysis of V heavy chain subgroup 5

											CDRI									
amino acid[1]	21	22	23	24	25	26	27	28	29	30	31	A	B	32	33	34	35	36	37	38
A				3	2					4							8		1	
B																				
C		96						1			1									
D								2			2						1			
E						2					1									
F					3		6		97					2						
G				92		93					1						72			
H											1			4						1
I										4						93				
K			89					1												
L															1				2	
M			1													1			1	
N			1					2		4	14			2						
P					1															1
Q			4																	
R			1			1		2							1					95
S	94			1	90			84		10	61			2	2		15			
T	2							5		75	16					2	1			
V																1			93	
W															93			97		
X																				
Y							90							87						
Z																				
-												97	97							
unknown (?)																				
not sequenced	1	1	1	1	1	1	1													
sum of seq[2]	96	96	96	96	96	96	96	97	97	97	97	97	97	97	97	97	97	97	97	97
oomcaa[3]	94	96	89	92	90	93	90	84	97	75	61	97	97	87	93	93	72	97	93	95
mcaa[4]	S	C	K	G	S	G	Y	S	F	T	S	-	-	Y	W	I	G	W	V	R
rel. oomcaa[5]	98%	100%	93%	96%	94%	97%	94%	87%	100%	77%	63%	100%	100%	90%	96%	96%	74%	100%	96%	98%
pos occupied[6]	2	1	5	3	4	3	2	7	1	5	8	1	1	5	4	4	5	1	4	3

Table 6F: Analysis of V heavy chain subgroup 5

	Framework II																			
amino acid[1]	39	40	41	42	43	44	45	46	47	48	49	50	51	52	A	B	C	53	54	55
A			1			1									1			2	1	
B																				
C														1				1		
D														14				8	93	
E					3			97											2	
F												1		2						
G				97		96					95							69	1	
H														3	1					
I										1		75	92							
K		1			94															
L							94			2		2	1							
M		92								89			1							
N																				
P			96				2							1	93					1
Q	97						1													
R		1									1	14						1		
S												1			1			16		96
T		1										3	1		1					
V		2								5	1	1	2							
W									94											
X																				
Y									3					76						
Z																				
-																97	97			
unknown (?)																				
not sequenced																				
sum of seq[2]	97	97	97	97	97	97	97	97	97	97	97	97	97	97	97	97	97	97	97	97
oomcaa[3]	97	92	96	97	94	96	94	97	94	89	95	75	92	76	93	97	97	69	93	96
mcaa[4]	Q	M	P	G	K	G	L	E	W	M	G	I	I	Y	P	-	-	G	D	S
rel. oomcaa[5]	100%	95%	99%	100%	97%	99%	97%	100%	97%	92%	98%	77%	95%	78%	96%	100%	100%	71%	96%	99%
pos occupied[6]	1	5	2	1	2	2	3	1	2	4	3	7	5	6	5	1	1	6	4	2

Table 6F: Analysis of V heavy chain subgroup 5

	CDR II																			
amino acid[1]	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75
A		6					1									88				
B																				
C					1					1										
D	77									2							97			
E	3								2									2		
F				2				91				1		3						
G	1									94										
H											15									
I		4	1					1				3		88						91
K			2															93		
L						1		4							2					
M														3						1
N	2		14	2																
P						95	1		1										1	
Q									91		81							1		
R			78						3		1			1				1		
S	2	2			95	1	95	1					1		95				96	1
T		85	2		1								96							4
V				1								93		2		9				
W																				
X																				
Y	12			92																
Z																				
-																				
unknown (?)																				
not sequenced																				
sum of seq[2]	97	97	97	97	97	97	97	97	97	97	97	97	97	97	97	97	97	97	97	97
oomcaa[3]	77	85	78	92	95	95	95	91	91	94	81	93	96	88	95	88	97	93	96	91
mcaa[4]	D	T	R	Y	S	P	S	F	Q	G	Q	V	T	I	S	A	D	K	S	I
rel. oomcaa[5]	79%	88%	80%	95%	98%	98%	98%	94%	94%	97%	84%	96%	99%	91%	98%	91%	100%	96%	99%	94%
pos occupied[6]	6	4	5	4	3	3	3	4	4	3	3	3	2	5	2	2	1	4	2	4

Table 6F: Analysis of V heavy chain subgroup 5

	Framework III																			
amino acid[1]	76	77	78	79	80	81	82	A	B	C	83	84	85	86	87	88	89	90	91	92
A		1	91								1	96				93				
B																				
C							1													95
D				1										96						
E						1					1									
F				1														2	6	
G								3	1							4				
H						3														
I															2		9			
K											91						1			
L					96					97							2			
M																	84			
N	7							2	2						2					
P			1																	
Q						93														
R	1						1	1	3		3									
S	87	2	1	1				90	91				96		5					
T	2	94	2					1			1	1	1		88		1			
V			2		1									1						
W							95													
X																				
Y				94														94	89	
Z																				
-																				
unknown (?)																				
not sequenced																		1	2	2
sum of seq[2]	97	97	97	97	97	97	97	97	97	97	97	97	97	97	97	97	97	96	95	95
oomcaa[3]	87	94	91	94	96	93	95	90	91	97	91	96	96	96	88	93	84	94	89	95
mcaa[4]	S	T	A	Y	L	Q	W	S	S	L	K	A	S	D	T	A	M	Y	Y	C
rel. oomcaa[5]	90%	97%	94%	97%	99%	96%	98%	93%	94%	100%	94%	99%	99%	99%	91%	96%	87%	98%	94%	100%
pos occupied[6]	4	3	5	4	2	3	3	5	4	1	5	2	2	2	4	2	5	2	2	1

Table 6F: Analysis of V heavy chain subgroup 5

	CDR III																			
amino acid[1]	93	94	95	96	97	98	99	100	A	B	C	D	E	F	G	H	I	J	K	101
A	92		1	1	2		3	4	3	2		1			1			4		2
B																				
C						1	1	1			2		1							
D				3	3	3	3	1	2	1	1	2		2	1	1	2			37
E			1	1	1	2			1	1				1			1			
F					1		3			3	2		1						26	
G			1	9	11	12	12	5	2	4	3	10	2	1				5		
H			10	1		2			1	1		1								
I				3		2	2	1	1	4	1	1		1	1					
K		1	1	1		1	3	1								2				
L			11	2	3	1	1	2	5		1		1		1					
M					2	1	1		1	1	1	1							10	
N				1		2		1	1	2			1					2		
P			5	1	4	3	1	2				1	1	1	1					
Q		1	3	2		1	1	4	2	1	2									3
R		92	7	9	2	2		2	1		2									
S		1	1	3	2	6	4	4	5	3	5	3	2	2			1		1	
T	1		1	3	2	1	2	6	3	3	6	1		1						
V	2		2	4	4		1		1	2			1							
W			1		2	1					1		2		1		1	1		
X																				
Y				1	6	3	6	9	8	7	2	1	2	6	8	9	9	10		1
Z																				
-						1	1	2	8	10	16	23	30	30	31	32	30	22	7	2
unknown (?)													1			1	1	1		
not sequenced	2	2	52	52	52	52	52	52	52	52	52	52	52	52	52	52	52	52	53	52
sum of seq[2]	95	95	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	44	45
oomcaa[3]	92	92	11	9	11	12	12	9	8	10	16	23	30	30	31	32	30	22	26	37
mcaa[4]	A	R	L	G	G	G	G	Y	Y	-	-	-	-	-	-	-	-	-	F	D
rel. oomcaa[5]	97%	97%	24%	20%	24%	27%	27%	20%	18%	22%	36%	51%	67%	67%	69%	71%	67%	49%	59%	82%
pos occupied[6]	3	4	13	16	14	18	16	15	16	15	14	11	11	9	8	4	6	6	4	5

Table 6F: Analysis of V heavy chain subgroup 5

	Framework IV												
amino acid[1]	102	103	104	105	106	107	108	109	110	111	112	113	sum
A												1	611
B													
C													205
D	1												458
E				1									404
F	2												256
G			41		41								1065
H													44
I	9								2				588
K				3									650
L	2						25	1					549
M							8						303
N													64
P	2					1					1		414
Q				34									612
R				3									351
S	2										40	39	1545
T	1					40	8		39				604
V	11							40		41			594
W		43											432
X													
Y	13												738
Z													
-	2												635
unknown (?)													4
not sequenced	52	54	56	56	56	56	56	56	56	56	56	57	1678
sum of seq[2]	45	43	41	41	41	41	41	41	41	41	41	40	
oomcaa[3]	13	43	41	34	41	40	25	40	39	41	40	39	
mcaa[4]	Y	W	G	Q	G	T	L	V	T	V	S	S	
rel. oomcaa[5]	29%	100%	100%	83%	100%	98%	61%	98%	95%	100%	98%	98%	
pos occupied[6]	10	1	1	4	1	2	3	2	2	1	2	2	

Table 6G: Analysis of V heavy chain subgroup 6

	Framework I																			
amino acid[1]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
A												1								
B																				
C																				
D																				
E																				
F																				
G								52		67										
H																				
I																				
K													68							
L				52							68	1						67	1	68
M																				
N																				
P									68					67					1	
Q	52		52		51	52										68				
R					1					1										
S							52							1	68				66	
T																	68			
V		52										66						1		
W																				
X																				
Y																				
Z																				
-																				
unknown (?)																				
not sequenced	22	22	22	22	22	22	22	22	6	6	6	6	6	6	6	6	6	6	6	6
sum of seq[2]	52	52	52	52	52	52	52	52	68	68	68	68	68	68	68	68	68	68	68	68
oomcaa[3]	52	52	52	52	51	52	52	52	68	67	68	66	68	67	68	68	68	67	66	68
mcaa[4]	Q	V	Q	L	Q	Q	S	G	P	G	L	V	K	P	S	Q	T	L	S	L
rel. oomcaa[5]	100%	100%	100%	100%	98%	100%	100%	100%	100%	99%	100%	97%	100%	99%	100%	100%	100%	99%	97%	100%
pos occupied[6]	1	1	1	1	2	1	1	1	1	2	1	3	1	2	1	1	1	2	3	1

Table 6G: Analysis of V heavy chain subgroup 6

											CDRI									
amino acid[1]	21	22	23	24	25	26	27	28	29	30	31	A	B	32	33	34	35	36	37	38
A	1		67											66	67					
B																				
C		68																		
D							68				1						1			
E																				
F										2				1	1				1	
G			1			69							3	1	2					
H																	1			
I				64								2					1		70	
K												3								
L																				
M																				
N							1				2	66					70			
P																				
Q																				
R											2	1								74
S	1			1	69			69		68	66		67		3		1			
T	67										2	1	4		1					
V			1	4					70					6					2	
W		1														74		74		
X																				
Y												1							1	
Z																				
-																				
unknown (?)											1									
not sequenced	5	5	5	5	5	5	5	5	4	4										
sum of seq[2]	69	69	69	69	69	69	69	69	70	70	74	74	74	74	74	74	74	74	74	74
oomcaa[3]	67	68	67	64	69	69	68	69	70	68	66	66	67	66	67	74	70	74	70	74
mcaa[4]	T	C	A	I	S	G	D	S	V	S	S	N	S	A	A	W	N	W	I	R
rel. oomcaa[5]	97%	99%	97%	93%	100%	100%	99%	100%	100%	97%	89%	89%	91%	89%	91%	100%	95%	100%	95%	100%
pos occupied[6]	3	2	3	3	1	1	2	1	1	2	5	6	3	4	5	1	5	1	4	1

Table 6G: Analysis of V heavy chain subgroup 6

	Framework II																			
amino acid[1]	39	40	41	42	43	44	45	46	47	48	49	50	51	52	A	B	C	53	54	55
A				1									1					1		
B																				
C																				
D																				
E								74												
F														2	1			1		
G						74					74	1							1	
H															1					
I																				
K	1				1											1			66	
L	1						74			74										
M																				
N																			1	
P			73																	
Q	72																			
R					73							73				72			1	1
S		74	1	73												1		72		
T													73						5	
V																				
W									74											73
X																				
Y														72	72					
Z																				
-																	74			
unknown (?)																				
not sequenced																				
sum of seq[2]	74	74	74	74	74	74	74	74	74	74	74	74	74	74	74	74	74	74	74	74
oomcaa[3]	72	74	73	73	73	74	74	74	74	74	74	73	73	72	72	72	74	72	66	73
mcaa[4]	Q	S	P	S	R	G	L	E	W	L	G	R	T	Y	Y	R	-	S	K	W
rel. oomcaa[5]	97%	100%	99%	99%	99%	100%	100%	100%	100%	100%	100%	99%	99%	97%	97%	97%	100%	97%	89%	99%
pos occupied[6]	3	1	2	2	2	1	1	1	1	1	1	2	2	2	3	3	1	3	5	2

Table 6G: Analysis of V heavy chain subgroup 6

	CDR II																			
amino acid[1]	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75
A					73	1							2			6		1		
B																				
C				1																
D			68			1									2		73			
E	1		3			7			1											2
F	7																			
G			1				1			8										
H	1																1			
I						1						65	2	71				1		
K		1							67						1					70
L	1					5		2				4						1		
M												1								
N	2	65	1						1						69					
P					1	1										66				
Q									2		1									
R		1							3		73									
S	2	2	1	1			73			66			1		2	1			73	
T		4											69	1				71	1	2
V						58		72				4		2		1				
W																				
X																				
Y	60	1		72																
Z																				
-																				
unknown (?)																				
not sequenced																				
sum of seq[2]	74	74	74	74	74	74	74	74	74	74	74	74	74	74	74	74	74	74	74	74
oomcaa[3]	60	65	68	72	73	58	73	72	67	66	73	65	69	71	69	66	73	71	73	70
mcaa[4]	Y	N	D	Y	A	V	S	V	K	S	R	I	T	I	N	P	D	T	S	K
rel. oomcaa[5]	81%	88%	92%	97%	99%	78%	99%	97%	91%	89%	99%	88%	93%	96%	93%	89%	99%	96%	99%	95%
pos occupied[6]	7	6	5	3	2	7	2	2	5	2	2	4	4	3	4	4	2	4	2	3

Table 6G: Analysis of V heavy chain subgroup 6

	Framework III																			
amino acid[1]	76	77	78	79	80	81	82	A	B	C	83	84	85	86	87	88	89	90	91	92
A													1			74				
B																				
C																				73
D								3						73						
E													73							
F			71						1										3	
G														1						
H						2		1												
I			1														2			
K								4												
L		1			74		72													
M							1			1							2			
N	74							63											1	
P												70								
Q		72				71														
R		1				1		1												1
S				74				1	73		1	3								
T								1			73				74			1		
V			2				1			73							70			
W																				
X																				
Y																		73	70	
Z																				
-																				
unknown (?)																				
not sequenced												1								
sum of seq[2]	74	74	74	74	74	74	74	74	74	74	74	73	74	74	74	74	74	74	74	74
oomcaa[3]	74	72	71	74	74	71	72	63	73	73	73	70	73	73	74	74	70	73	70	73
mcaa[4]	N	Q	F	S	L	Q	L	N	S	V	T	P	E	D	T	A	V	Y	Y	C
rel. oomcaa[5]	100%	97%	96%	100%	100%	96%	97%	85%	99%	99%	99%	96%	99%	99%	100%	100%	95%	99%	95%	99%
pos occupied[6]	1	3	3	1	1	3	3	7	2	2	2	2	2	2	1	1	3	2	3	2

Table 6G: Analysis of V heavy chain subgroup 6

amino acid[1]	93	94	95	96	97	98	99	100	A	B	C	D	E	F	G	H	I	J	K	101
	CDR III																			
A	69		11	1	3	12	4	3	2	5		8						10	1	
B																				
C					1		1			1		1	1							
D			19	4	3	7	4	3	1	6	1	1	1							62
E			10	4	2	1	2	2	1	2							1			
F	1		1	1	1		1	2	3		2			1					38	4
G	1		16	4	15	15	11	8	6	2	5	1	8	6	1			17		
H				1		1			1	1	1	1				1	1	1		
I				1	2		2		5	1										
K		1	1	1	1	1	1	1				1								
L			1	8	4	2	3	2	1					1	5				8	
M				1				1			5								11	
N			1	3	1	2	1	1	1	3		2		1		1	3			
P				10	4		5	3		5	1		1							
Q			1	1	1	1					1									1
R		69	1	7	8	1	8	8	3		1	1	5							1
S		3	5	5	5	7	6	7	3	4	2					1	1			
T			1	1	4	3	4	4	6	3	1			1						
V	3	1	4	5	1	9			4		9	5	1	1					2	
W			1	6	8		3	2	4								4	4		
X																				
Y				6	4	2	2	2	6	6	2	4	2	1	8	8	12	12		
Z																				
-				2	3	7	14	23	25	33	41	47	53	54	57	56	50	28	12	4
unknown (?)														6	1	5				
not sequenced				1	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1
sum of seq[2]	74	74	73	72	71	71	72	72	72	72	72	72	72	72	72	72	72	72	72	72
oomcaa[3]	69	69	19	10	15	15	14	23	25	33	41	47	53	54	57	56	50	28	38	62
mcaa[4]	A	R	D	P	G	G	-	-	-	-	-	-	-	-	-	-	-	-	F	D
rel. oomcaa[5]	93%	93%	26%	14%	21%	21%	19%	32%	35%	46%	57%	65%	74%	75%	79%	78%	69%	39%	53%	86%
pos occupied[6]	4	4	14	20	19	15	17	16	16	13	13	11	8	8	4	5	7	6	6	5

Table 6G: Analysis of V heavy chain subgroup 6

amino acid[1]	Framework IV 102	103	104	105	106	107	108	109	110	111	112	113	sum
A							2						494
B													
C													147
D								1					403
E													186
F	2										2		150
G			49		50								571
H	2												18
I	9					3		1					304
K				1			1						293
L	5						26						632
M							8						31
N													436
P	4			6								1	387
Q				40									539
R				2									495
S	4		1			1					43	46	1271
T						45	4		45				640
V	21						2	46		48			647
W		65					5						398
X													
Y	19												518
Z													
-	2												585
unknown (?)													13
not sequenced	5	8	23	24	23	24	25	25	28	25	28	26	580
sum of seq[2]	68	65	50	49	50	49	48	48	45	48	45	47	
oomcaa[3]	21	65	49	40	50	45	26	46	45	48	43	46	
mcaa[4]	V	W	G	Q	G	T	L	V	T	V	S	S	
rel. oomcaa[5]	31%	100%	98%	82%	100%	92%	54%	96%	100%	100%	96%	98%	
pos occupied[6]	9	1	2	4	1	3	7	3	1	1	2	2	

Appendix to Tables 1A-C

A. References of rearranged sequences

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Claims

1. A method of setting up one or more nucleic acid sequences encoding one or more (poly)peptide sequences suitable for the creation of libraries of (poly)peptides said (poly)peptide sequences comprising amino acid consensus sequences, said method comprising the following steps:
   (a) deducing from a collection of at least three homologous proteins one or more (poly)peptide sequences comprising at least one amino acid consensus sequence;
   (b) optionally, identifying amino acids in said (poly)peptide sequences to be modified so as to remove unfavorable interactions between amino acids within or between said or other (poly)peptide sequences;
   (c) identifying at least one structural sub-element within each of said (poly)peptide sequences;
   (d) backtranslating each of said (poly)peptide sequences into a corresponding coding nucleic acid sequence;
   (e) setting up cleavage sites in regions adjacent to or between the ends of sub-sequences encoding said sub-elements, each of said cleavage sites:
      (ea) being unique within each of said coding nucleic acid sequences;
      (eb) being common to the corresponding sub-sequences of any said coding nucleic acids.

2. A method of setting up two or more sets of one or more nucleic acid sequences comprising executing the steps described in claim 1 for each of said sets with the additional provision that said cleavage sites are unique between said sets.

3. The method of claim 2 in which at least two of said sets are deduced from the same collection of at least three homologous proteins.

4. The method according to any one of claims 1 to 3, wherein said setting up further comprises the synthesis of said nucleic acid coding sequences.

5. The method according to any one of claims 1 to 4, further comprising the cloning of said nucleic acid coding sequences into a vector.

6. The method according to any one of claims 1 to 5, wherein said removal of unfavorable interactions results in enhanced expression of said (poly)peptides.

7. The method according to any one of claims 1 to 6, further comprising the steps of:
   (f) cleaving at least two of said cleavage sites located in regions adjacent to or between the ends of said sub-sequences; and
   (g) exchanging said sub-sequences by different sequences; and
   (h) optionally, repeating steps (f) and (g) one or more times.

8. The method according to claim 7, wherein said different sequences are selected from the group of different sub-sequences encoding the same or different sub-elements derived from the same or different (poly)peptides.

9. The method according to claims 7 or 8, wherein said different sequences are selected from the group of:
   (i) genomic sequences or sequences derived from genomic sequences;
   (ii) rearranged genomic sequences or sequences derived from rearranged genomic sequences; and
   (iii) random sequences.

10. The method according to any one of claims 1 to 9 further comprising the expression of said nucleic acid coding sequences.

11. The method according to any one of claims 1 to 10 further comprising the steps of:
   (i) screening, after expression, the resultant (poly)peptides for a desired property;
   (k) optionally, repeating steps (f) to (i) one or more times with nucleic acid sequences encoding one or more (poly)peptides obtained in step (i).

12. The method according to claim 11, wherein said desired property is selected from the group of optimized affinity or specificity for a target molecule, optimized enzymatic activity, optimized expression yields, optimized stability and optimized solubility.

13. The method according to any one of claims 1 to 12, wherein said cleavage sites are sites cleaved by restriction enzymes.

14. The method according to any one of claims 1 to 13, wherein said structural sub-elements comprise between 1 and 150 amino acids.

15. The method according to claim 14, wherein said structural sub-elements comprise between 3 and 25 amino acids.

16. The method according to any one of claims 1 to 15, wherein said nucleic acid is DNA.

17. The method according to any one of claims 1 to 16, wherein said (poly)peptides have an amino acid pattern characteristic of a particular species.

18. The method according to claim 17, wherein said species is human.

19. The method according to any one of claims 1 to 18, wherein said (poly)peptides are at least part of members or derivatives of the immunoglobulin superfamily.

20. The method according to claim 19, wherein said members or derivatives of the immunoglobulin superfamily are members or derivatives of the immunoglobulin family.

21. The method according to claim 19 or 20, wherein said (poly)peptides are or are derived from heavy or light chain variable regions wherein said structural sub-elements are framework regions (FR) 1, 2, 3, or 4 or complementary determining regions (CDR) 1, 2, or 3.

22. The method according to claim 20 or 21, wherein said (poly)peptides are or are derived from the HuCAL consensus genes:
Vκ1, Vκ2, Vκ3, Vκ4, Vλ1, Vλ2, Vλ3, VH1A, VH1B, VH2, VH3, VH4, VH5, VH6, Cκ, Cλ, CH1 or any combination of said HuCAL consensus genes.

23. The method according to any one of claims 20 to 22, wherein said derivative of said immunoglobulin family or said combination is an Fv, disulphide-linked Fv, single-chain Fv (scFv), or Fab fragment.

24. The method according to claims 22 to 23, wherein said derivative is an scFv fragment comprising the combination of HuCAL VH3 and HuCAL Vλ2 consensus genes that comprises a random sub-sequence encoding the heavy chain CDR3 sub-element.

25. The method according to any one of claims 1 to 24, wherein at least part of said (poly)peptide sequences or (poly)peptides is connected to a sequence encoding at least one additional moiety or to at least one additional moiety, respectively.

26. The method according to claim 25, wherein said connection is formed via a contiguous nucleic acid sequence or amino acid sequence, respectively.

27. The method according to claims 25 to 26, wherein said additional moiety is a toxin, a cytokine, a reporter enzyme, a moiety being capable of binding a metal ion, a peptide, a tag suitable for detection and/or purification, or a homo- or hetero-association domain.

28. The method according to any one of claims 10 to 27, wherein the expression of said nucleic acid sequences results in the generation of a repertoire of biological activities and/or specificities, preferably in the generation of a repertoire based on a universal framework.

29. A nucleic acid sequence obtainable by the method according to any of claims 1 to 28.

30. A collection of nucleic acid sequences obtainable by the method according to any of claims 1 to 28.

31. A recombinant vector obtainable by the method according to any of claims 5 to 28.

32. A collection of recombinant vectors obtainable by the method according to any of claims 5 to 30.

33. A host cell transformed with the recombinant vector according to claim 31.

34. A collection of host cells transformed with the collection of recombinant vectors according to claim 32.

35. A method of producing a (poly)peptide or a collection of (poly)peptides as defined in any of claims 1 to 28 comprising culturing the host cell according to claim 33 or the collection of host cells according to claim 34 under suitable conditions and isolating said (poly)peptide or said collection of (poly)peptides.

36. A (poly)peptide devisable by the method according to any one of claims 1 to 3, encoded by the nucleic acid sequence according to claim 29 or obtainable by the method according to any one of claims 4 to 28 or 35.

37. A collection of (poly)peptides devisable by the method according to any one of claims 1 to 3, encoded by the collection of nucleic acid sequences according to claim 30 or obtainable by the method according to any one of claims 4 to 28 or 35.

38. A vector suitable for use in the method according to any of claims 5 to 28 and 35 characterized in that said vector is essentially devoid of any cleavage site as defined in claim 1(e) and 2.

39. The vector according to claim 38 which is an expression vector.

40. A kit comprising at least one of:
(a) a nucleic acid sequence according to claim 29;
(b) a collection of nucleic acid sequences according to claim 30;
(c) a recombinant vector according to claim 31;
(d) a collection of recombinant vectors according to claim 32;
(e) a (poly)peptide according to claim 36;
(f) a collection of (poly)peptides according to claim 37;
(g) a vector according to claim 38 or 39; and optionally,

(h) a suitable host cell for carrying out the method according to claim 35.

41. A method of designing two or more genes encoding a collection of two or more proteins, comprising the steps of:

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(a) either

(aa) identifying two or more homologous gene sequences, or

(ab) analyzing at least three homologous genes, and

deducing two or more consensus gene sequences therefrom,

(b) optionally, modifying codons in said consensus gene sequences to remove unfavourable interactions between amino acids in the resulting proteins,

(c) identifying sub-sequences which encode structural sub-elements in said consensus gene sequences

(d) modifying one or more bases in regions adjacent to or between the ends of said sub-sequences to define one or more cleavage sites, each of which:

(da) are unique within each consensus gene sequence,

(db) do not form compatible sites with respect to any single sub-sequence,

(dc) are common to all homologous sub-sequences.

42. A method of preparing two or more genes encoding a collection of two or more proteins, comprising the steps of :

(a) designing said genes according to claim 41, and

(b) synthesizing said genes.

43. A collection of genes prepared according to the method of claim 42.

44. A collection of two or more genes derived from gene sequences which:

(a) are either homologous, or represent consensus gene sequences derived from at least three homologous genes, and

(b) carry cleavage sites, each of which:

(ba) lie at or adjacent to the ends of genetic sub-sequences which encode structural sub-elements,

(bb) are unique within each gene sequence,

(bc) do not form compatible sites with respect to any single sub-sequence, and

(bd) are common to all homologous sub-sequences.

45. The collection of genes according to either of claims 43 or 44 in which each of said gene sequences has a nucleotide composition characteristic of a particular species.

46. The collection of genes according to claim 45 in which said species is human.

47. The collection of genes according to any of claims 43 to 46 in which one or more of said gene sequences encodes at least part of a member of the immunoglobulin superfamily, preferably of the immunoglobulin family.

48. The collection of genes according to claim 47 in which said structural sub-elements correspond to any combination of framework regions 1, 2, 3, and 4, and/or CDR regions 1, 2, and 3 of antibody heavy chains.

49. The collection of genes according to claim 47 in which said structural sub-elements correspond to any combination of framework regions 1, 2, 3, and 4, and/or CDR regions 1, 2, and 3 of antibody light chains.

50. A collection of vectors comprising a collection of gene sequences according to any of claims 43 to 49.

51. The collection of vectors according to claim 50 comprising the additional feature that the vector does not comprise any cleavage site that is contained in the collection of genes according to any of claims 43 to 49.

52. A method for identifying one or more genes encoding one or more proteins having a desirable property, comprising the steps of:

(a) expressing from the collection of vectors according to either of claims 50 or 51 a collection of proteins.

(b) screening said collection to isolate one or more proteins having a desired property,

(c) identifying the genes encoding the proteins isolated in step (b),

(d) optionally, excising from the genes encoding the proteins isolated in step (b) one or more genetic sub-sequences encoding structural sub-elements, and replacing said sub-sequence(s) by one or more second sub-sequences encoding structural sub-elements, to generate new vectors according to either of claims 50 or 51,

(e) optionally, repeating steps (a) to (c).

53. A method for identifying one or more genes encoding one or more antibody fragments which binds to a target, comprising the steps of:

(a) expressing from the collection of vectors according to either of claims 50 or 51 a collection of proteins,

(b) screening said collection to isolate one or more antibody fragments which bind to said target,

(c) identifying the genes encoding the proteins isolated in step (b),

(d) optionally, excising from the genes encoding the antibody fragments isolated in step (b) one or more genetic sub-sequences encoding structural sub-elements, and replacing said sub-sequence(s) by one or

more second sub-sequences encoding structural sub-generate new vectors according to either of claims 50 or 51,

(e) optionally, repeating steps (a) to (c).

54. A kit comprising two or more genes derived from gene sequences which:

(a) are either homologous, or represent consensus gene sequences derived from at least three homologous genes, and

(b) carry cleavage sites, each of which:

(ba) lie at or adjacent to the ends of genetic sub-sequences which encode structural sub-elements,

(bb) are unique within each gene sequence,

(bc) do not form compatible sites with respect to any single sub-sequence, and

(bd) are common to all homologous sub-sequences.

55. A kit comprising two or more genetic sub-sequences which encode structural sub-elements, which can be assembled to form genes, and which carry cleavage sites, each of which:

(a) lie at or adjacent to the ends of said genetic sub-sequences,

(b) do not form compatible sites with respect to any single sub-sequence, and

(d) are common to all homologous sub-sequences.

Figure 1: construction of a synthetic human antibody library based on consensus sequences

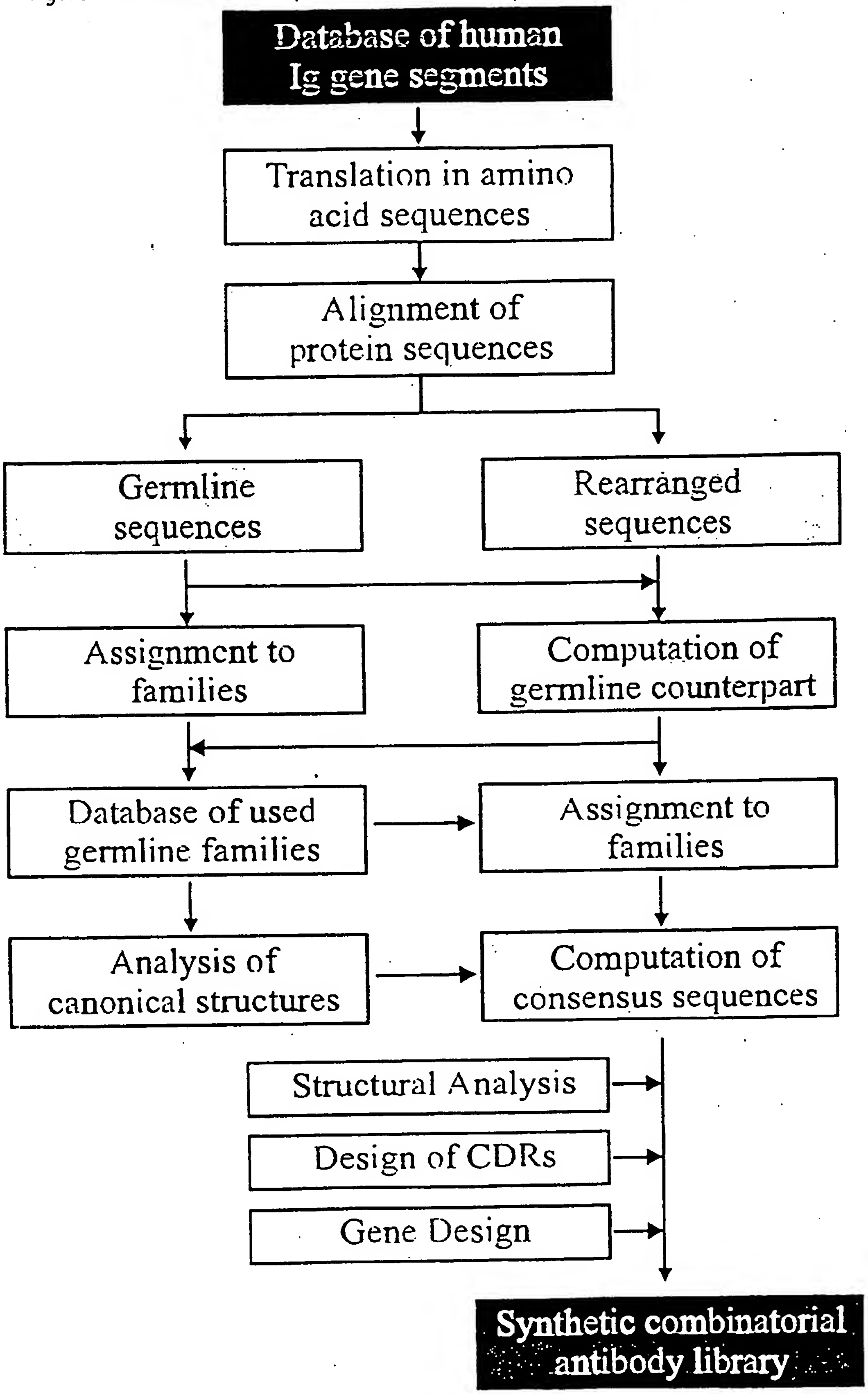

Figure 2A: VL kappa consensus sequences

	framework 1																							CDRI						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	A	B	C
Vκ1	D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T	I	T	C	R	A	S	Q	-	-	-
Vκ2	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	Q	S	L	L
Vκ3	D	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T	L	S	C	R	A	S	Q	S	-	-
Vκ4	D	I	V	M	T	Q	S	P	D	S	L	A	V	S	L	G	E	R	A	T	I	N	C	R	S	S	Q	S	V	L

	CDRI										framework 2															CDR II				
	D	E	F	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54
Vκ1	-	-	-	G	I	S	S	Y	L	A	W	Y	Q	Q	K	P	G	K	A	P	K	L	L	I	Y	A	A	S	S	L
Vκ2	H	S	-	N	G	Y	N	Y	L	D	W	Y	L	Q	K	P	G	Q	S	P	Q	L	L	I	Y	L	G	S	N	R
Vκ3	-	-	-	V	S	S	S	Y	L	A	W	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	G	A	S	S	R
Vκ4	Y	S	S	N	N	K	N	Y	L	A	W	Y	Q	Q	K	P	G	Q	P	P	K	L	L	I	Y	W	A	S	T	R

Figure 2A: VL kappa consensus sequences

	CDRII		framework 3																											
	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84
Vκ1	Q	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q	P	E	D	F	A
Vκ2	A	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V	E	A	E	D	V	G
Vκ3	A	T	G	V	P	A	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	E	P	E	D	F	A
Vκ4	E	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q	A	E	D	V	A

	framework 3				CDRIII								framework 4												
	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107	108	109
Vκ1	T	Y	Y	C	Q	Q	H	Y	T	T	P	P	T	F	G	Q	G	T	K	V	E	I	K	R	T
Vκ2	V	Y	Y	C	Q	Q	H	Y	T	T	P	P	T	F	G	Q	G	T	K	V	E	I	K	R	T
Vκ3	V	Y	Y	C	Q	Q	H	Y	T	T	P	P	T	F	G	Q	G	T	K	V	E	I	K	R	T
Vκ4	V	Y	Y	C	Q	Q	H	Y	T	T	P	P	T	F	G	Q	G	T	K	V	E	I	K	R	T

Figure 2B: VL lambda consensus sequences

	framework 1																							CDRI						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	D	E	28
Vλ1	Q	S	V	L	T	Q	P	P	S	-	V	S	G	A	P	G	Q	R	V	T	I	S	C	S	G	S	S	S	N	I
Vλ2	Q	S	A	L	T	Q	P	A	S	-	V	S	G	S	P	G	Q	S	I	T	I	S	C	T	G	T	S	S	D	V
Vλ3	S	Y	E	L	T	Q	P	P	S	-	V	S	V	A	P	G	Q	T	A	R	I	S	C	S	G	D	A	-	-	L

	CDRI							framework 2															CDR II							
	29	30	31	A	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57
Vλ1	G	S	N	-	Y	V	S	W	Y	Q	Q	L	P	G	T	A	P	K	L	L	I	Y	D	N	N	Q	R	P	S	G
Vλ2	G	G	Y	N	Y	V	S	W	Y	Q	Q	H	P	G	K	A	P	K	L	M	I	Y	D	V	S	N	R	P	S	G
Vλ3	G	D	K	-	Y	A	S	W	Y	Q	Q	K	P	G	Q	A	P	V	L	V	I	Y	D	D	S	D	R	P	S	G

Figure 2B: VL lambda consensus sequences

	framework 3																													
	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87
Vλ1	V	P	D	R	F	S	G	S	K	S	G	T	S	A	S	L	A	I	T	G	L	Q	S	E	D	E	A	D	Y	Y
Vλ2	V	S	N	R	F	S	G	S	K	S	G	N	T	A	S	L	T	I	S	G	L	Q	A	E	D	E	A	D	Y	Y
Vλ3	I	P	E	R	F	S	G	S	N	S	G	N	T	A	T	L	T	I	S	G	T	Q	A	E	D	E	A	D	Y	Y

		CDRIII								framework 4											
	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	A	107
Vλ1	C	Q	Q	H	Y	T	T	P	P	V	F	G	G	G	T	K	L	T	V	L	G
Vλ2	C	Q	Q	H	Y	T	T	P	P	V	F	G	G	G	T	K	L	T	V	L	G
Vλ3	C	Q	Q	H	Y	T	T	P	P	V	F	G	G	G	T	K	L	T	V	L	G

Figure 2C: V heavy chain consensus sequences

	framework 1																													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
VH1A	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	C	K	A	S	G	G	T	F	S
VH1B	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	A	S	V	K	V	S	C	K	A	S	G	Y	T	F	T
VH2	Q	V	Q	L	K	E	S	G	P	A	L	V	K	P	T	Q	T	L	T	L	T	C	T	F	S	G	F	S	L	S
VH3	E	V	Q	L	V	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	A	S	G	F	T	F	S
VH4	Q	V	Q	L	Q	E	S	G	P	G	L	V	K	P	S	E	T	L	S	L	T	C	T	V	S	G	G	S	I	S
VH5	E	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	E	S	L	K	I	S	C	K	G	S	G	Y	S	F	T
VH6	Q	V	Q	L	Q	Q	S	G	P	G	L	V	K	P	S	Q	T	L	S	L	T	C	A	I	S	G	D	S	V	S

	CDRI								framework 2														CDR II									
	31	A	B	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	A	B	C	53	54	55	56	57
VH1A	S	-	-	Y	A	I	S	W	V	R	Q	A	P	G	Q	G	L	E	W	M	G	G	I	I	P	-	-	I	F	G	T	A
VH1B	S	-	-	Y	Y	M	H	W	V	R	Q	A	P	G	Q	G	L	E	W	M	G	W	I	N	P	-	-	N	S	G	G	T
VH2	T	S	G	V	G	V	G	W	I	R	Q	P	P	G	K	A	L	E	W	L	A	L	I	D	-	-	-	W	D	D	D	K
VH3	S	-	-	Y	A	M	S	W	V	R	Q	A	P	G	K	G	L	E	W	V	S	A	I	S	G	-	-	S	G	G	S	T
VH4	S	-	-	Y	Y	W	S	W	I	R	Q	P	P	G	K	G	L	E	W	I	G	Y	I	Y	-	-	-	Y	S	G	S	T
VH5	S	-	-	Y	W	I	G	W	V	R	Q	M	P	G	K	G	L	E	W	M	G	I	I	Y	P	-	-	G	D	S	D	T
VH6	S	N	S	A	A	W	N	W	I	R	Q	S	P	G	R	G	L	E	W	L	G	R	T	Y	Y	R	-	S	K	W	Y	N

Figure 2C: V heavy chain consensus sequences

	CDRII										framework 3																				
	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	A	B	C	83	84	85
VH1A	N	Y	A	Q	K	F	Q	G	R	V	T	I	T	A	D	E	S	T	S	T	A	Y	M	E	L	S	S	L	R	S	E
VH1B	N	Y	A	Q	K	F	Q	G	R	V	T	M	T	R	D	T	S	I	S	T	A	Y	M	E	L	S	S	L	R	S	E
VH2	Y	Y	S	T	S	L	K	T	R	L	T	I	S	K	D	T	S	K	N	Q	V	V	L	T	M	T	N	M	D	P	V
VH3	Y	Y	A	D	S	V	K	G	R	F	T	I	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	S	L	R	A	E
VH4	N	Y	N	P	S	L	K	S	R	V	T	I	S	V	D	T	S	K	N	Q	F	S	L	K	L	S	S	V	T	A	A
VH5	R	Y	S	P	S	F	Q	G	Q	V	T	I	S	A	D	K	S	I	S	T	A	Y	L	Q	W	S	S	L	K	A	S
VH6	D	Y	A	V	S	V	K	S	R	I	T	I	N	P	D	T	S	K	N	Q	F	S	L	Q	L	N	S	V	T	P	E

	framework 3										CDRIII														framework 4							
	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	A	B	C	101	102	103	104	105	106	107	108	109	110	111	112	113
VH1A	D	T	A	V	Y	Y	C	A	R	W	G	G	D	G	F	Y	A	M	D	Y	W	G	Q	G	T	L	V	T	V	S	S
VH1B	D	T	A	V	Y	Y	C	A	R	W	G	G	D	G	F	Y	A	M	D	Y	W	G	Q	G	T	L	V	T	V	S	S
VH2	D	T	A	T	Y	Y	C	A	R	W	G	G	D	G	F	Y	A	M	D	Y	W	G	Q	G	T	L	V	T	V	S	S
VH3	D	T	A	V	Y	Y	C	A	R	W	G	G	D	G	F	Y	A	M	D	Y	W	G	Q	G	T	L	V	T	V	S	S
VH4	D	T	A	V	Y	Y	C	A	R	W	G	G	D	G	F	Y	A	M	D	Y	W	G	Q	G	T	L	V	T	V	S	S
VH5	D	T	A	M	Y	Y	C	A	R	W	G	G	D	G	F	Y	A	M	D	Y	W	G	Q	G	T	L	V	T	V	S	S
VH6	D	T	A	V	Y	Y	C	A	R	W	G	G	D	G	F	Y	A	M	D	Y	W	G	Q	G	T	L	V	T	V	S	S

Figure 3A: V kappa 1 (Vκ1) gene sequence

```
.D  I  Q  M   T  Q  S   P  S  S   L  S  A  S   V  G  D
 EcoRV              BanII
~~~~~~            ~~~~~~~~
GATATCCAGA TGACCCAGAG CCCGTCTAGC CTGAGCGCGA GCGTGGGTGA
CTATAGGTCT ACTGGGTCTC GGGCAGATCG GACTCGCGCT CGCACCCACT

  R  V  T   I  T  C  R   A  S  Q   G  I  S   S  Y  L
                  PstI
                ~~~~~~~~
TCGTGTGACC ATTACCTGCA GAGCGAGCCA GGGCATTAGC AGCTATCTGG
AGCACACTGG TAATGGACGT CTCGCTCGGT CCCGTAATCG TCGATAGACC

A  W  Y  Q   Q  K  P   G  K  A  P   K  L  L   I  Y  A
    KpnI            SexAI                  AseI
   ~~~~~~~        ~~~~~~~~~             ~~~~~~~~
CGTGGTACCA GCAGAAACCA GGTAAAGCAC CGAAACTATT AATTTATGCA
GCACCATGGT CGTCTTTGGT CCATTTCGTG GCTTTGATAA TTAAATACGT

 A  S  S  L   Q  S  G   V  P  S   R  F  S  G   S  G  S
                      SanDI                      BamHI
                    ~~~~~~~~~                    ~~~~~
GCCAGCAGCT TGCAAAGCGG GGTCCCGTCC CGTTTTAGCG GCTCTGGATC
```

Figure 3A: V kappa 1 (Vκ1) gene sequence (continued)

```
CGGTCGTCGA ACGTTTCGCC CCAGGGCAGG GCAAAATCGC CGAGACCTAG

  G  T  D   F  T  L  T   I  S  S   L  Q  P   E  D  F
                                          Eco57I
                                          ~~~~~~~~
BamHI                                        BbsI
~                                            ~~~~~~~
CGGCACTGAT TTTACCCTGA CCATTAGCAG CCTGCAACCT GAAGACTTTG
GCCGTGACTA AAATGGGACT GGTAATCGTC GGACGTTGGA CTTCTGAAAC

A  T  Y  Y   C  Q  Q   H  Y  T  T   P  P  T   F  G  Q
                                                MscI
                                               ~~~~~~~
CGACCTATTA TTGCCAGCAG CATTATACCA CCCCGCCGAC CTTTGGCCAG
GCTGGATAAT AACGGTCGTC GTAATATGGT GGGGCGGCTG GAAACCGGTC

 G  T  K  V   E  I  K   R  T
                        BsiWI
                        ~~~~~~
GGTACGAAAG TTGAAATTAA ACGTACG
CCATGCTTTC AACTTTAATT TGCATGC
```

Figure 3B: V kappa 2 (Vκ2) gene sequence

```
 D  I  V  M   T  Q  S   P  L  S   L  P  V  T   P  G  E
 EcoRV               BanII
~~~~~~             ~~~~~~~~
GATATCGTGA TGACCCAGAG CCCACTGAGC CTGCCAGTGA CTCCGGGCGA
CTATAGCACT ACTGGGTCTC GGGTGACTCG GACGGTCACT GAGGCCCGCT

  P  A  S  I  S  C  R   S  S  Q   S  L  L   H  S  N
                PstI
              ~~~~~~~~
GCCTGCGAGC ATTAGCTGCA GAAGCAGCCA AAGCCTGCTG CATAGCAACG
CGGACGCTCG TAATCGACGT CTTCGTCGGT TTCGGACGAC GTATCGTTGC

G  Y  N  Y   L  D  W   Y  L  Q  K   P  G  Q   S  P  Q
                  KpnI            SexAI
                ~~~~~~~~        ~~~~~~~~
GCTATAACTA TCTGGATTGG TACCTTCAAA AACCAGGTCA AAGCCCGCAG
CGATATTGAT AGACCTAACC ATGGAAGTTT TTGGTCCAGT TTCGGGCGTC

 L  L  I  Y   L  G  S   N  R  A   S  G  V  P   D  R  F
   AseI                              SanDI
 ~~~~~~                            ~~~~~~~~~
CTATTAATTT ATCTGGGCAG CAACCGTGCC AGTGGGGTCC CGGATCGTTT
GATAATTAAA TAGACCCGTC GTTGGCACGG TCACCCCAGG GCCTAGCAAA
```

Figure 3B: V kappa 2 (Vκ2) gene sequence (continued)

```
  S  G  S   G  S  G  T   D  F  T   L  K  I   S  R  V
            BamHI
           ~~~~~~~
TAGCGGCTCT GGATCCGGCA CCGATTTTAC CCTGAAAATT AGCCGTGTGG
ATCGCCGAGA CCTAGGCCGT GGCTAAAATG GGACTTTTAA TCGGCACACC

E  A  E  D   V  G  V   Y  Y  C  Q   Q  H  Y   T  T  P
   Eco57I
   ~~~~~~~
      BbsI
     ~~~~~~~~
AAGCTGAAGA CGTGGGCGTG TATTATTGCC AGCAGCATTA TACCACCCCG
TTCGACTTCT GCACCCGCAC ATAATAACGG TCGTCGTAAT ATGGTGGGGC

 P  T  F  G   Q  G  T   K  V  E   I  K  R  T
        MscI                            BsiWI
       ~~~~~~~~                        ~~~~~~~
CCGACCTTTG GCCAGGGTAC GAAAGTTGAA ATTAAACGTA CG
GGCTGGAAAC CGGTCCCATG CTTTCAACTT TAATTTGCAT GC
```

Figure 3C: V kappa 3 (Vκ3) gene sequence

```
 D   I   V   L   T   Q   S    P   A   T    L   S   L   S    P   G   E
 EcoRV                    BanII
~~~~~~~                 ~~~~~~~~
GATATCGTGC TGACCCAGAG CCCGGCGACC CTGAGCCTGT CTCCGGGCGA
CTATAGCACG ACTGGGTCTC GGGCCGCTGG GACTCGGACA GAGGCCCGCT

  R   A   T    L   S   C   R    A   S   Q    S   V   S    S   S   Y
                     PstI
                   ~~~~~~~~
ACGTGCGACC CTGAGCTGCA GAGCGAGCCA GAGCGTGAGC AGCAGCTATC
TGCACGCTGG GACTCGACGT CTCGCTCGGT CTCGCACTCG TCGTCGATAG

L   A   W   Y    Q   Q   K    P   G   Q   A    P   R   L    L   I   Y
      KpnI              SexAI                      AseI
    ~~~~~~~~         ~~~~~~~~~                   ~~~~~~~
TGGCGTGGTA CCAGCAGAAA CCAGGTCAAG CACCGCGTCT ATTAATTTAT
ACCGCACCAT GGTCGTCTTT GGTCCAGTTC GTGGCGCAGA TAATTAAATA

 G   A   S   S    R   A   T    G   V   P    A   R   F   S    G   S   G
                                 SanDI                        BamHI
                               ~~~~~~~~                          ~~
GGCGCGAGCA GCCGTGCAAC TGGGGTCCCG GCGCGTTTTA GCGGCTCTGG
```

Figure 3C: V kappa 3 (Vκ3) gene sequence (continued)

```
CCGCGCTCGT CGGCACGTTG ACCCCAGGGC CGCGCAAAAT CGCCGAGACC

 S  G  T   D  F  T  L   T  I  S   S  L  E   P  E  D
                                            Eco57I
                                            ~~~~~~~
                                               BbsI
BamHI                                         ~~~~~~~
~~~~
ATCCGGCACG GATTTTACCC TGACCATTAG CAGCCTGGAA CCTGAAGACT
TAGGCCGTGC CTAAAATGGG ACTGGTAATC GTCGGACCTT GGACTTCTGA

F  A  V  Y   Y  C  Q   Q  H  Y  T   T  P  P   T  F  G
                                                 MscI
                                                 ~~~~
TTGCGGTGTA TTATTGCCAG CAGCATTATA CCACCCCGCC GACCTTTGGC
AACGCCACAT AATAACGGTC GTCGTAATAT GGTGGGGCGG CTGGAAACCG

 Q  G  T  K   V  E  I   K  R  T
MscI                     BsiWI
~~                      ~~~~~~~
CAGGGTACGA AAGTTGAAAT TAAACGTACG
GTCCCATGCT TTCAACTTTA ATTTGCATGC
```

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Figure 3D: V kappa 4 (Vκ4) gene sequence

```
 D  I  V  M   T  Q  S   P  D  S   L  A  V  S   L  G  E
 EcoRV               BanII
~~~~~~~             ~~~~~~~~
GATATCGTGA TGACCCAGAG CCCGGATAGC CTGGCGGTGA GCCTGGGCGA
CTATAGCACT ACTGGGTCTC GGGCCTATCG GACCGCCACT CGGACCCGCT

  R  A  T   I  N  C  R   S  S  Q   S  V  L   Y  S  S
                 PstI
               ~~~~~~~~
ACGTGCGACC ATTAACTGCA GAAGCAGCCA GAGCGTGCTG TATAGCAGCA
TGCACGCTGG TAATTGACGT CTTCGTCGGT CTCGCACGAC ATATCGTCGT

N  N  K  N   Y  L  A   W  Y  Q  Q   K  P  G   Q  P  P
                        KpnI          SexAI
                      ~~~~~~~       ~~~~~~~~~
ACAACAAAAA CTATCTGGCG TGGTACCAGC AGAAACCAGG TCAGCCGCCG
TGTTGTTTTT GATAGACCGC ACCATGGTCG TCTTTGGTCC AGTCGGCGGC

 K  L  L  I   Y  W  A   S  T  R   E  S  G  V   P  D  R
    AseI                                SanDI
   ~~~~~~~~                           ~~~~~~~~~
AAACTATTAA TTTATTGGGC ATCCACCCGT GAAAGCGGGG TCCCGGATCG
TTTGATAATT AAATAACCCG TAGGTGGGCA CTTTCGCCCC AGGGCCTAGC
```

Figure 3D: V kappa 4 (Vκ4) gene sequence (continued)

```
  F   S   G    S   G   S   G    T   D   F    T   L   T    I   S   S
                       BamHI
                      ~~~~~~~
TTTTAGCGGC TCTGGATCCG GCACTGATTT TACCCTGACC ATTTCGTCCC
AAAATCGCCG AGACCTAGGC CGTGACTAAA ATGGGACTGG TAAAGCAGGG

L   Q   A   E    D   V   A    V   Y   Y   C    Q   Q   H    Y   T   T
          Eco57I
         ~~~~~~~~
            BbsI
           ~~~~~~~~
TGCAAGCTGA AGACGTGGCG GTGTATTATT GCCAGCAGCA TTATACCACC
ACGTTCGACT TCTGCACCGC CACATAATAA CGGTCGTCGT AATATGGTGG

 P   P   T   F    G   Q   G    T   K   V    E   I   K   R    T
                 MscI                                   BsiWI
                ~~~~~~~                               ~~~~~~~
CCGCCGACCT TTGGCCAGGG TACGAAAGTT GAAATTAAAC GTACG
GGCGGCTGGA AACCGGTCCC ATGCTTTCAA CTTTAATTTG CATGC
```

Figure 4A: V lambda 1 (Vλ1) gene sequence

```
Q  S  V  L  T  Q  P  P  S  V  S  G  A  P  G  Q  R
                                     SexAI
                                   ~~~~~~~~~
CAGAGCGTGC TGACCCAGCC GCCTTCAGTG AGTGGCGCAC CAGGTCAGCG
GTCTCGCACG ACTGGGTCGG CGGAAGTCAC TCACCGCGTG GTCCAGTCGC
                         Eco57I
                         ~~~~~~

V  T  I  S  C  S  G  S  S  S  N  I  G  S  N  Y
         BssSI
       ~~~~~~~~
TGTGACCATC TCGTGTAGCG GCAGCAGCAG CAACATTGGC AGCAACTATG
ACACTGGTAG AGCACATCGC CGTCGTCGTC GTTGTAACCG TCGTTGATAC

V  S  W  Y  Q  Q  L  P  G  T  A  P  K  L  L  I  Y
      KpnI           XmaI   BbeI
    ~~~~~~~~        ~~~~~~ ~~~~~~~~
TGAGCTGGTA CCAGCAGTTG CCCGGGACGG CGCCGAAACT GCTGATTTAT
ACTCGACCAT GGTCGTCAAC GGGCCCTGCC GCGGCTTTGA CGACTAAATA

D  N  N  Q  R  P  S  G  V  P  D  R  F  S  G  S  K
               Bsu36I                         BamHI
              ~~~~~~~~~                      ~~~~~~
```

Figure 4A: V lambda 1 (Vλ1) gene sequence (continued)

```
GATAACAACC AGCGTCCCTC AGGCGTGCCG GATCGTTTTA GCGGATCCAA
CTATTGTTGG TCGCAGGGAG TCCGCACGGC CTAGCAAAAT CGCCTAGGTT

  S  G  T   S  A  S  L   A  I  T   G  L  Q   S  E  D
                                                 BbsI
                                                ~~~~~~
AAGCGGCACC AGCGCGAGCC TTGCGATTAC GGGCCTGCAA AGCGAAGACG
TTCGCCGTGG TCGCGCTCGG AACGCTAATG CCCGGACGTT TCGCTTCTGC

E  A  D  Y   Y  C  Q   Q  H  Y  T   T  P  P   V  F  G
AAGCGGATTA TTATTGCCAG CAGCATTATA CCACCCCGCC TGTGTTTGGC
TTCGCCTAAT AATAACGGTC GTCGTAATAT GGTGGGGCGG ACACAAACCG

 G  G  T  K   L  T  V   L  G
             HpaI       MscI
            ~~~~~~~     ~~~
GGCGGCACGA AGTTAACCGT TCTTGGC
CCGCCGTGCT TCAATTGGCA AGAACCG
```

Figure 4B: V lambda 2 (Vλ2) gene sequence

```
 Q  S  A  L   T  Q  P  A  S  V   S  G  S  P   G  Q  S
                                           SexAI
                                          ~~~~~~~~~
CAGAGCGCAC TGACCCAGCC AGCTTCAGTG AGCGGCTCAC CAGGTCAGAG
GTCTCGCGTG ACTGGGTCGG TCGAAGTCAC TCGCCGAGTG GTCCAGTCTC
                        Eco57I
                        ~~~~~~~

  I  T  I  S  C  T  G   T  S  S   D  V  G   G  Y  N
            BssSI
           ~~~~~~~~
CATTACCATC TCGTGTACGG GTACTAGCAG CGATGTGGGC GGCTATAACT
GTAATGGTAG AGCACATGCC CATGATCGTC GCTACACCCG CCGATATTGA

 Y  V  S  W   Y  Q  Q   H  P  G  K   A  P  K   L  M  I
            KpnI            XmaI       BbeI
           ~~~~~~~~        ~~~~~~~    ~~~~~~~
ATGTGAGCTG GTACCAGCAG CATCCCGGGA AGGCGCCGAA ACTGATGATT
TACACTCGAC CATGGTCGTC GTAGGGCCCT TCCGCGGCTT TGACTACTAA

  Y  D  V  S   N  R  P   S  G  V   S  N  R  F   S  G  S
                     Bsu36I                        BamHI
                    ~~~~~~~~~                      ~~~~~
TATGATGTGA GCAACCGTCC CTCAGGCGTG AGCAACCGTT TTAGCGGATC
ATACTACACT CGTTGGCAGG GAGTCCGCAC TCGTTGGCAA AATCGCCTAG
```

Figure 4B: V lambda 2 (Vλ2) gene sequence (continued)

```
  K  S  G   N  T  A  S   L  T  I   S  G  L   Q  A  E
BamHI                                              BbsI
~                                                  ~~~~
CAAAAGCGGC AACACCGCGA GCCTGACCAT TAGCGGCCTG CAAGCGGAAG
GTTTTCGCCG TTGTGGCGCT CGGACTGGTA ATCGCCGGAC GTTCGCCTTC

D  E  A  D   Y  Y  C   Q  Q  H  Y   T  T  P   P  V  F
BbsI
~~
ACGAAGCGGA TTATTATTGC CAGCAGCATT ATACCACCCC GCCTGTGTTT
TGCTTCGCCT AATAATAACG GTCGTCGTAA TATGGTGGGG CGGACACAAA

 G  G  G  T   K  L  T   V  L  G
               HpaI        MscI
             ~~~~~~~       ~~~~
GGCGGCGGCA CGAAGTTAAC CGTTCTTGGC
CCGCCGCCGT GCTTCAATTG GCAAGAACCG
```

Figure 4C: V lambda 3 (Vλ3) gene sequence

```
 S   Y   E   L    T   Q   P    P   S   V    S   V   A   P    G   Q   T
                                                         SexAI
                                                       ~~~~~~~~~
AGCTATGAAC TGACCCAGCC GCCTTCAGTG AGCGTTGCAC CAGGTCAGAC
TCGATACTTG ACTGGGTCGG CGGAAGTCAC TCGCAACGTG GTCCAGTCTG
                        Eco57I
                        ~~~~~~

  A   R   I    S   C   S   G    D   A   L    G   D   K    Y   A   S
              BssSI
            ~~~~~~~~
CGCGCGTATC TCGTGTAGCG GCGATGCGCT GGGCGATAAA TACGCGAGCT
GCGCGCATAG AGCACATCGC CGCTACGCGA CCCGCTATTT ATGCGCTCGA

W   Y   Q   Q    K   P   G    Q   A   P   V    L   V   I    Y   D   D
 KpnI              XmaI      BbeI
~~~~~~           ~~~~~~    ~~~~~~
GGTACCAGCA GAAACCCGGG CAGGCGCCAG TTCTGGTGAT TTATGATGAT
CCATGGTCGT CTTTGGGCCC GTCCGCGGTC AAGACCACTA AATACTACTA
```

Figure 4C: V lambda 3 (Vλ3) gene sequence (continued)

```
 S  D  R  P   S  G  I   P  E  R   F  S  G  S   N  S  G
             Bsu36I                         BamHI
             ~~~~~~~~                     ~~~~~~~~
TCTGACCGTC CCTCAGGCAT CCCGGAACGC TTTAGCGGAT CCAACAGCGG
AGACTGGCAG GGAGTCCGTA GGGCCTTGCG AAATCGCCTA GGTTGTCGCC

  N  T  A   T  L  T  I   S  G  T   Q  A  E   D  E  A
                                        BbsI
                                      ~~~~~~~~
CAACACCGCG ACCCTGACCA TTAGCGGCAC TCAGGCGGAA GACGAAGCGG
GTTGTGGCGC TGGGACTGGT AATCGCCGTG AGTCCGCCTT CTGCTTCGCC

D  Y  Y  C   Q  Q  H   Y  T  T  P   P  V  F   G  G  G
ATTATTATTG CCAGCAGCAT TATACCACCC CGCCTGTGTT TGGCGGCGGC
TAATAATAAC GGTCGTCGTA ATATGGTGGG GCGGACACAA ACCGCCGCCG

 T  K  L  T   V  L  G
      HpaI       MscI
    ~~~~~~~~     ~~~~
ACGAAGTTAA CCGTTCTTGG C
TGCTTCAATT GGCAAGAACC G
```

Figure 5A: V heavy chain 1A (VH1A) gene sequence

```
  Q  V  Q  L   V  Q  S   G  A  E   V  K  K  P   G  S  S
     MfeI
    ~~~~~~~~
CAGGTGCAAT TGGTTCAGTC TGGCGCGGAA GTGAAAAAAC CGGGCAGCAG
GTCCACGTTA ACCAAGTCAG ACCGCGCCTT CACTTTTTTG GCCCGTCGTC

  V  K  V   S  C  K  A   S  G  G   T  F  S   S  Y  A
                          BspEI
                         ~~~~~~~
CGTGAAAGTG AGCTGCAAAG CCTCCGGAGG CACTTTTAGC AGCTATGCGA
GCACTTTCAC TCGACGTTTC GGAGGCCTCC GTGAAAATCG TCGATACGCT

 I  S  W  V   R  Q  A   P  G  Q  G   L  E  W   M  G  G
                 BstXI               XhoI
             ~~~~~~~~~~~~~~         ~~~~~~
TTAGCTGGGT GCGCCAAGCC CCTGGGCAGG GTCTCGAGTG GATGGGCGGC
AATCGACCCA CGCGGTTCGG GGACCCGTCC CAGAGCTCAC CTACCCGCCG

  I  I  P  I   F  G  T   A  N  Y   A  Q  K  F   Q  G  R
ATTATTCCGA TTTTTGGCAC GGCGAACTAC GCGCAGAAGT TTCAGGGCCG
TAATAAGGCT AAAAACCGTG CCGCTTGATG CGCGTCTTCA AAGTCCCGGC

  V  T  I   T  A  D  E   S  T  S   T  A  Y   M  E  L
BstEII
```

Figure 5A: V heavy chain 1A (VH1A) gene sequence (continued)

```
~~~~~~~~
GGTGACCATT  ACCGCGGATG  AAAGCACCAG  CACCGCGTAT  ATGGAACTGA
CCACTGGTAA  TGGCGCCTAC  TTTCGTGGTC  GTGGCGCATA  TACCTTGACT

 S   S   L   R    S   E   D   T   A   V   Y    Y   C   A    R   W   G
                                EagI                BssHII
                               ~~~~~~~              ~~~~~~~~
GCAGCCTGCG  TAGCGAAGAT  ACGGCCGTGT  ATTATTGCGC  GCGTTGGGGC
CGTCGGACGC  ATCGCTTCTA  TGCCGGCACA  TAATAACGCG  CGCAACCCCG

  G   D   G   F    Y   A   M    D   Y   W    G   Q   G   T    L   V   T
                                               StyI
                                              ~~~~~~~
GGCGATGGCT  TTTATGCGAT  GGATTATTGG  GGCCAAGGCA  CCCTGGTGAC
CCGCTACCGA  AAATACGCTA  CCTAATAACC  CCGGTTCCGT  GGGACCACTG

   V   S   S
      BlpI
     ~~~~~~~
GGTTAGCTCA  G
CCAATCGAGT  C
```

Figure 5B: V heavy chain 1B (VH1B) gene sequence

```
 Q  V  Q  L   V  Q  S   G  A  E   V  K  K  P   G  A  S
      MfeI
     ~~~~~~~~
CAGGTGCAAT TGGTTCAGAG CGGCGCGGAA GTGAAAAAAC CGGGCGCGAG
GTCCACGTTA ACCAAGTCTC GCCGCGCCTT CACTTTTTTG GCCCGCGCTC

  V  K  V   S  C  K  A   S  G  Y   T  F  T   S  Y  Y
                          BspEI
                         ~~~~~~~
CGTGAAAGTG AGCTGCAAAG CCTCCGGATA TACCTTTACC AGCTATTATA
GCACTTTCAC TCGACGTTTC GGAGGCCTAT ATGGAAATGG TCGATAATAT

M  H  W  V   R  Q  A   P  G  Q  G   L  E  W   M  G  W
                BstXI                XhoI
             ~~~~~~~~~~~~~~         ~~~~~~~
TGCACTGGGT CCGCCAAGCC CCTGGGCAGG GTCTCGAGTG GATGGGCTGG
ACGTGACCCA GGCGGTTCGG GGACCCGTCC CAGAGCTCAC CTACCCGACC

 I  N  P  N   S  G  G   T  N  Y   A  Q  K  F   Q  G  R
ATTAACCCGA ATAGCGGCGG CACGAACTAC GCGCAGAAGT TTCAGGGCCG
TAATTGGGCT TATCGCCGCC GTGCTTGATG CGCGTCTTCA AAGTCCCGGC
```

Figure 5B: V heavy chain 1B (VH1B) gene sequence (continued)

```
  V  T  M  T  R  D  T  S  I  S  T  A  Y  M  E  L
BstEII
~~~~~~~~
GGTGACCATG ACCCGTGATA CCAGCATTAG CACCGCGTAT ATGGAACTGA
CCACTGGTAC TGGGCACTAT GGTCGTAATC GTGGCGCATA TACCTTGACT

S  S  L  R  S  E  D  T  A  V  Y  Y  C  A  R  W  G
                      EagI             BssHII
                     ~~~~~~~          ~~~~~~~~
GCAGCCTGCG TAGCGAAGAT ACGGCCGTGT ATTATTGCGC GCGTTGGGGC
CGTCGGACGC ATCGCTTCTA TGCCGGCACA TAATAACGCG CGCAACCCCG

 G  D  G  F  Y  A  M  D  Y  W  G  Q  G  T  L  V  T
                                  StyI
                                ~~~~~~~
GGCGATGGCT TTTATGCGAT GGATTATTGG GGCCAAGGCA CCCTGGTGAC
CCGCTACCGA AAATACGCTA CCTAATAACC CCGGTTCCGT GGGACCACTG

  V  S  S
    BlpI
   ~~~~~~~
GGTTAGCTCA G
CCAATCGAGT C
```

Figure 5C: V heavy chain 2 (VH2) gene sequence

```
 Q   V   Q   L    K   E   S    G   P   A    L   V   K   P    T   Q   T
        MfeI
       ~~~~~~~~
CAGGTGCAAT TGAAAGAAAG CGGCCCGGCC CTGGTGAAAC CGACCCAAAC
GTCCACGTTA ACTTTCTTTC GCCGGGCCGG GACCACTTTG GCTGGGTTTG

  L   T   L    T   C   T   F    S   G   F    S   L   S    T   S   G
                               BspEI
                              ~~~~~~~
CCTGACCCTG ACCTGTACCT TTTCCGGATT TAGCCTGTCC ACGTCTGGCG
GGACTGGGAC TGGACATGGA AAAGGCCTAA ATCGGACAGG TGCAGACCGC

V   G   V   G    W   I   R    Q   P   P   G    K   A   L    E   W   L
                                 BstXI              XhoI
                          ~~~~~~~~~~~~~~~~      ~~~~~~~~
TTGGCGTGGG CTGGATTCGC CAGCCGCCTG GGAAAGCCCT CGAGTGGCTG
AACCGCACCC GACCTAAGCG GTCGGCGGAC CCTTTCGGGA GCTCACCGAC

 A   L   I   D    W   D   D    D   K   Y    Y   S   T   S    L   K   T
                                                                MluI
                                                                  ~~
GCTCTGATTG ATTGGGATGA TGATAAGTAT TATAGCACCA GCCTGAAAAC
CGAGACTAAC TAACCCTACT ACTATTCATA ATATCGTGGT CGGACTTTTG
```

Figure 5C: V heavy chain 2 (VH2) gene sequence (continued)

```
 R  L  T   I  S  K  D   T  S  K   N  Q  V   V  L  T
MluI                      NspV
~~~~                     ~~~~~~~
GCGTCTGACC ATTAGCAAAG ATACTTCGAA AAATCAGGTG GTGCTGACTA
CGCAGACTGG TAATCGTTTC TATGAAGCTT TTTAGTCCAC CACGACTGAT

M  T  N  M   D  P  V   D  T  A  T   Y  Y  C   A  R  W
                                          BssHII
                                          ~~~~~~~~
TGACCAACAT GGACCCGGTG GATACGGCCA CCTATTATTG CGCGCGTTGG
ACTGGTTGTA CCTGGGCCAC CTATGCCGGT GGATAATAAC GCGCGCAACC

 G  G  D  G   F  Y  A   M  D  Y   W  G  Q  G   T  L  V
                                     StyI
                                   ~~~~~~~~
GGCGGCGATG GCTTTTATGC GATGGATTAT TGGGGCCAAG GCACCCTGGT
CCGCCGCTAC CGAAAATACG CTACCTAATA ACCCCGGTTC CGTGGGACCA

  T  V  S   S
      BlpI
     ~~~~~~~
GACGGTTAGC TCAG
CTGCCAATCG AGTC
```

Figure 5D: V heavy chain 3 (VH3) gene sequence

```
 E  V  Q  L   V  E  S   G  G  G   L  V  Q  P   G  G  S
       MfeI
     ~~~~~~~~
GAAGTGCAAT TGGTGGAAAG CGGCGGCGGC CTGGTGCAAC CGGGCGGCAG
CTTCACGTTA ACCACCTTTC GCCGCCGCCG GACCACGTTG GCCCGCCGTC

 L  R  L   S  C  A  A   S  G  F   T  F  S   S  Y  A
                        BspEI
                       ~~~~~~~
CCTGCGTCTG AGCTGCGCGG CCTCCGGATT TACCTTTAGC AGCTATGCGA
GGACGCAGAC TCGACGCGCC GGAGGCCTAA ATGGAAATCG TCGATACGCT

M  S  W  V   R  Q  A   P  G  K  G   L  E  W   V  S  A
                 BstXI              XhoI
             ~~~~~~~~~~~~~~~      ~~~~~~~
TGAGCTGGGT GCGCCAAGCC CCTGGGAAGG GTCTCGAGTG GGTGAGCGCG
ACTCGACCCA CGCGGTTCGG GGACCCTTCC CAGAGCTCAC CCACTCGCGC

 I  S  G  S   G  G  S   T  Y  Y   A  D  S  V   K  G  R
ATTAGCGGTA GCGGCGGCAG CACCTATTAT GCGGATAGCG TGAAAGGCCG
TAATCGCCAT CGCCGCCGTC GTGGATAATA CGCCTATCGC ACTTTCCGGC
```

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Figure 5D: V heavy chain 3 (VH3) gene sequence (continued)

```
 F  T  I   S  R  D  N   S  K  N   T  L  Y   L  Q  M
             PmlI          NspV
           -------      -------
TTTTACCATT TCACGTGATA ATTCGAAAAA CACCCTGTAT CTGCAAATGA
AAAATGGTAA AGTGCACTAT TAAGCTTTTT GTGGGACATA GACGTTTACT

N  S  L  R   A  E  D   T  A  V  Y   Y  C  A   R  W  G
                         EagI          BssHII
                       -------       --------
ACAGCCTGCG TGCGGAAGAT ACGGCCGTGT ATTATTGCGC GCGTTGGGGC
TGTCGGACGC ACGCCTTCTA TGCCGGCACA TAATAACGCG CGCAACCCCG

 G  D  G  F   Y  A  M   D  Y  W   G  Q  G  T   L  V  T
                                      StyI
                                    -------
GGCGATGGCT TTTATGCGAT GGATTATTGG GGCCAAGGCA CCCTGGTGAC
CCGCTACCGA AAATACGCTA CCTAATAACC CCGGTTCCGT GGGACCACTG

 V  S  S
     BlpI
    -------
GGTTAGCTCA G
CCAATCGAGT C
```

Figure 5E: V heavy chain 4 (VH4) gene sequence

```
 Q  V  Q  L   Q  E  S   G  P  G   L  V  K  P   S  E  T
       MfeI
      ~~~~~~~~
CAGGTGCAAT TGCAAGAAAG TGGTCCGGGC CTGGTGAAAC CGAGCGAAAC
GTCCACGTTA ACGTTCTTTC ACCAGGCCCG GACCACTTTG GCTCGCTTTG

  L  S  L   T  C  T  V   S  G  G   S  I  S   S  Y  Y
                         BspEI
                        ~~~~~~~
CCTGAGCCTG ACCTGCACCG TTTCCGGAGG CAGCATTAGC AGCTATTATT
GGACTCGGAC TGGACGTGGC AAAGGCCTCC GTCGTAATCG TCGATAATAA

W  S  W  I   R  Q  P   P  G  K  G   L  E  W   I  G  Y
                BstXI               XhoI
             ~~~~~~~~~~~~~~~       ~~~~~~~
GGAGCTGGAT TCGCCAGCCG CCTGGGAAGG GTCTCGAGTG GATTGGCTAT
CCTCGACCTA AGCGGTCGGC GGACCCTTCC CAGAGCTCAC CTAACCGATA

 I  Y  Y  S   G  S  T   N  Y  N   P  S  L  K   S  R  V
                                                BstEII
                                                   ~~~
ATTTATTATA GCGGCAGCAC CAACTATAAT CCGAGCCTGA AAAGCCGGGT
TAAATAATAT CGCCGTCGTG GTTGATATTA GGCTCGGACT TTTCGGCCCA
```

Figure 5E: V heavy chain 4 (VH4) gene sequence (continued)

```
  T  I  S   V  D  T  S   K  N  Q   F  S  L   K  L  S
BstEII                NspV
~~~~                ~~~~~~~~
GACCATTAGC GTTGATACTT CGAAAAACCA GTTTAGCCTG AAACTGAGCA
CTGGTAATCG CAACTATGAA GCTTTTTGGT CAAATCGGAC TTTGACTCGT

S  V  T  A   A  D  T   A  V  Y  Y   C  A  R   W  G  G
                     EagI               BssHII
                   ~~~~~~~~           ~~~~~~
GCGTGACGGC GGCGGATACG GCCGTGTATT ATTGCGCGCG TTGGGGCGGC
CGCACTGCCG CCGCCTATGC CGGCACATAA TAACGCGCGC AACCCCGCCG

 D  G  F  Y   A  M  D   Y  W  G   Q  G  T  L   V  T  V
                                  StyI
                                ~~~~~~~~
GATGGCTTTT ATGCGATGGA TTATTGGGGC CAAGGCACCC TGGTGACGGT
CTACCGAAAA TACGCTACCT AATAACCCCG GTTCCGTGGG ACCACTGCCA

  S  S
   BlpI
  ~~~~~
TAGCTCAG
ATCGAGTC
```

Figure 5F: V heavy chain 5 (VH5) gene sequence

```
 E  V  Q  L   V  Q  S   G  A  E   V  K  K  P   G  E  S
          MfeI
        ~~~~~~~~
GAAGTGCAAT TGGTTCAGAG CGGCGCGGAA GTGAAAAAAC CGGGCGAAAG
CTTCACGTTA ACCAAGTCTC GCCGCGCCTT CACTTTTTTG GCCCGCTTTC

  L  K  I   S  C  K  G   S  G  Y   S  F  T   S  Y  W
                          BspEI
                         ~~~~~~~
CCTGAAAATT AGCTGCAAAG GTTCCGGATA TTCCTTTACG AGCTATTGGA
GGACTTTTAA TCGACGTTTC CAAGGCCTAT AAGGAAATGC TCGATAACCT

 I  G  W  V   R  Q  M   P  G  K  G   L  E  W   M  G  I
                 BstXI              XhoI
             ~~~~~~~~~~~~~~       ~~~~~~
TTGGCTGGGT GCGCCAGATG CCTGGGAAGG GTCTCGAGTG GATGGGCATT
AACCGACCCA CGCGGTCTAC GGACCCTTCC CAGAGCTCAC CTACCCGTAA

  I  Y  P  G   D  S  D   T  R  Y   S  P  S  F   Q  G  Q
ATTTATCCGG GCGATAGCGA TACCCGTTAT TCTCCGAGCT TTCAGGGCCA
TAAATAGGCC CGCTATCGCT ATGGGCAATA AGAGGCTCGA AAGTCCCGGT
```

Figure 5F: V heavy chain 5 (VH5) gene sequence (continued)

```
  V  T  I   S  A  D  K   S  I  S   T  A  Y   L  Q  W
 BstEII
 ~~~~~~~~
 GGTGACCATT AGCGCGGATA AAAGCATTAG CACCGCGTAT CTTCAATGGA
 CCACTGGTAA TCGCGCCTAT TTTCGTAATC GTGGCGCATA GAAGTTACCT

 S  S  L  K   A  S  D   T  A  M  Y   Y  C  A   R  W  G
                                         BssHII
                                         ~~~~~~~~
 GCAGCCTGAA AGCGAGCGAT ACGGCCATGT ATTATTGCGC GCGTTGGGGC
 CGTCGGACTT TCGCTCGCTA TGCCGGTACA TAATAACGCG CGCAACCCCG

  G  D  G  F   Y  A  M   D  Y  W   G  Q  G  T   L  V  T
                                      StyI
                                     ~~~~~~~
 GGCGATGGCT TTTATGCGAT GGATTATTGG GGCCAAGGCA CCCTGGTGAC
 CCGCTACCGA AAATACGCTA CCTAATAACC CCGGTTCCGT GGGACCACTG

  V  S  S
     BlpI
    ~~~~~~~
 GGTTAGCTCA G
 CCAATCGAGT C
```

Figure 5G: V heavy chain 6 (VH6) gene sequence

```
 Q  V  Q  L   Q  Q  S   G  P  G   L  V  K  P   S  Q  T
         MfeI
        ~~~~~~~~
CAGGTGCAAT TGCAACAGTC TGGTCCGGGC CTGGTGAAAC CGAGCCAAAC
GTCCACGTTA ACGTTGTCAG ACCAGGCCCG GACCACTTTG GCTCGGTTTG

  L  S  L   T  C  A  I   S  G  D   S  V  S   S  N  S
                          BspEI
                         ~~~~~~
CCTGAGCCTG ACCTGTGCGA TTTCCGGAGA TAGCGTGAGC AGCAACAGCG
GGACTCGGAC TGGACACGCT AAAGGCCTCT ATCGCACTCG TCGTTGTCGC

A  A  W  N   W  I  R   Q  S  P  G   R  G  L   E  W  L
                          BstXI             XhoI
                     ~~~~~~~~~~~~~~~     ~~~~~~~~
CGGCGTGGAA CTGGATTCGC CAGTCTCCTG GGCGTGGCCT CGAGTGGCTG
GCCGCACCTT GACCTAAGCG GTCAGAGGAC CCGCACCGGA GCTCACCGAC

 G  R  T  Y   Y  R  S   K  W  Y   N  D  Y  A   V  S  V
GGCCGTACCT ATTATCGTAG CAAATGGTAT AACGATTATG CGGTGAGCGT
CCGGCATGGA TAATAGCATC GTTTACCATA TTGCTAATAC GCCACTCGCA
```

Figure 5G: V heavy chain 6 (VH6) gene sequence (continued)

```
  K  S  R   I  T  I  N   P  D  T   S  K  N   Q  F  S
              BsaBI                NspV
          ~~~~~~~~~~~~~           ~~~~~~~
GAAAAGCCGG ATTACCATCA ACCCGGATAC TTCGAAAAAC CAGTTTAGCC
CTTTTCGGCC TAATGGTAGT TGGGCCTATG AAGCTTTTTG GTCAAATCGG

L  Q  L  N   S  V  T   P  E  D  T   A  V  Y   Y  C  A
                                     EagI         BssHII
                                  ~~~~~~~         ~~~~~
TGCAACTGAA CAGCGTGACC CCGGAAGATA CGGCCGTGTA TTATTGCGCG
ACGTTGACTT GTCGCACTGG GGCCTTCTAT GCCGGCACAT AATAACGCGC

 R  W  G  G   D  G  F   Y  A  M   D  Y  W  G   Q  G  T
BssHII                                          StyI
~                                             ~~~~~~~
CGTTGGGGCG GCGATGGCTT TTATGCGATG GATTATTGGG GCCAAGGCAC
GCAACCCCGC CGCTACCGAA AATACGCTAC CTAATAACCC CGGTTCCGTG

  L  V  T   V  S  S
             BlpI
           ~~~~~~~
CCTGGTGACG GTTAGCTCAG
GGACCACTGC CAATCGAGTC
```

Figure 6: oligonucleotides for gene synthesis

O1K1 5'- GAATGCATACGCTGATATCCAGATGACCCAGAG-CCCGTCTAGCCTGAGC -3'

O1K2 5'- CGCTCTGCAGGTAATGGTCACACGATCACCCAC-GCTCGCGCTCAGGCTAGACGGGC -3'

O1K3 5'- GACCATTACCTGCAGAGCGAGCCAGGGCATTAG-CAGCTATCTGGCGTGGTACCAGCAG -3'

O1K4 5'- CTTTGCAAGCTGCTGGCTGCATAAATTAATAGT-TTCGGTGCTTTACCTGGTTTCTGCTGGTACCACGCCAG -3'

O1K5 5'- CAGCCAGCAGCTTGCAAAGCGGGGTCCCGTCCC-GTTTTAGCGGCTCTGGATCCGGCACTGATTTTAC -3'

O1K6 5'- GATAATAGGTCGCAAAGTCTTCAGGTTGCAGGC-TGCTAATGGTCAGGGTAAAATCAGTGCCGGATCC -3'

O2K1 5'- CGATATCGTGATGACCCAGAGCCCACTGAGCCT-GCCAGTGACTCCGGGCGAGCC -3'

O2K2 5'- GCCGTTGCTATGCAGCAGGCTTTGGCTGCTTCT-GCAGCTAATGCTCGCAGGCTCGCCCGGAGTCAC -3'

O2K3 5'- CTGCTGCATAGCAACGGCTATAACTATCTGGAT-TGGTACCTTCAAAAACCAGGTCAAAGCCC -3'

O2K4 5'- CGATCCGGGACCCCACTGGCACGGTTGCTGCCC-AGATAAATTAATAGCTGCGGGCTTTGACCTGGTTTTTG -3'

O2K5 5'- AGTGGGGTCCCGGATCGTTTTAGCGGCTCTGGA-TCCGGCACCGATTTTACCCTGAAAATTAGCCGTGTG -3'

O2K6 5'- CCATGCAATAATACACGCCCACGTCTTCAGCTT-CCACACGGCTAATTTTCAGGG -3'

O3K1 5'- GAATGCATACGCTGATATCGTGCTGACCCAGAG-CCCGG -3'

O3K2 5'- CGCTCTGCAGCTCAGGGTCGCACGTTCGCCCGG-AGACAGGCTCAGGGTCGCCGGGCTCTGGGTCAGC -3'

O3K3 5'- CCCTGAGCTGCAGAGCGAGCCAGAGCGTGAGCA-GCAGCTATCTGGCGTGGTACCAG -3'

Figure 6: (continued)

O3K4 5'- GCACGGCTGCTCGCGCCATAAATTAATAGACGC-GGTGCTTGACCTGGTTTCTGCTGGTACCACGCCAGATAG -3'

O3K5 5'- GCGCGAGCAGCCGTGCAACTGGGGTCCCGGCGC-GTTTTAGCGGCTCTGGATCCGGCACGGATTTTAC -3'

O3K6 5'- GATAATACACCGCAAAGTCTTCAGGTTCCAGGC-TGCTAATGGTCAGGGTAAAATCCGTGCCGGATC -3'

O4K1 5'- GAATGCATACGCTGATATCGTGATGACCCAGAG-CCCGGATAGCCTGGCG -3'

O4K2 5'- GCTTCTGCAGTTAATGGTCGCACGTTCGCCCAG-GCTCACCGCCAGGCTATCCGGGC -3'

O4K3 5'- CGACCATTAACTGCAGAAGCAGCCAGAGCGTGC-TGTATAGCAGCAACAACAAAAACTATCTGGCGTGGTACCAG -3'

O4K4 5'- GATGCCCAATAAATTAATAGTTTCGGCGGCTGA-CCTGGTTTCTGCTGGTACCACGCCAGATAG -3'

O4K5 5'- AAACTATTAATTTATTGGGCATCCACCCGTGAA-AGCGGGGTCCCGGATCGTTTTAGCGGCTCTGGATCCGGCAC-3'

O4K6 5'- GATAATACACCGCCACGTCTTCAGCTTGCAGGG-ACGAAATGGTCAGGGTAAAATCAGTGCCGGATCCAGAGCC -3'

O1L1 5'- GAATGCATACGCTCAGAGCGTGCTGACCCAGCC-GCCTTCAGTGAGTGG -3'

O1L2 5'- CAATGTTGCTGCTGCTGCCGCTACACGAGATGG-TCACACGCTGACCTGGTGCGCCACTCACTGAAGGCGGC -3'

O1L3 5'- GGCAGCAGCAGCAACATTGGCAGCAACTATGTG-AGCTGGTACCAGCAGTTGCCCGGGAC -3'

O1L4 5'- CCGGCACGCCTGAGGGACGCTGGTTGTTATCAT-AAATCAGCAGTTTCGGCGCCGTCCCGGGCAACTGC -3'

O1L5 5'- CCCTCAGGCGTGCCGGATCGTTTTAGCGGATCC-AAAAGCGGCACCAGCGCGAGCCTTGCG -3'

Figure 6: (continued)

O1L6 5'- CCGCTTCGTCTTCGCTTTGCAGGCCCGTAATCG-CAAGGCTCGCGCTGG -3'

O2L1 5'- GAATGCATACGCTCAGAGCGCACTGACCCAGCC-AGCTTCAGTGAGCGGC -3'

O2L2 5'- CGCTGCTAGTACCCGTACACGAGATGGTAATGC-TCTGACCTGGTGAGCCGCTCACTGAAGCTGG -3'

O2L3 5'- GTACGGGTACTAGCAGCGATGTGGGCGGCTATA-ACTATGTGAGCTGGTACCAGCAGCATCCCGG -3'

O2L4 5'- CGCCTGAGGGACGGTTGCTCACATCATAAATCA-TCAGTTTCGGCGCCTTCCCGGGATGCTGCTGGTAC -3'

O2L5 5'- CAACCGTCCCTCAGGCGTGAGCAACCGTTTTAG-CGGATCCAAAAGCGGCAACACCGCGAGCC -3'

O2L6 5'- CCGCTTCGTCTTCCGCTTGCAGGCCGCTAATGG-TCAGGCTCGCGGTGTTGCCG -3'

O3L1 5'- GAATGCATACGCTAGCTATGAACTGACCCAGCC-GCCTTCAGTGAGCG -3'

O3L2 5'- CGCCCAGCGCATCGCCGCTACACGAGATACGCG-CGGTCTGACCTGGTGCAACGCTCACTGAAGGCGGC -3'

O3L3 5'- GGCGATGCGCTGGGCGATAAATACGCGAGCTGG-TACCAGCAGAAACCCGGGCAGGCGC -3'

O3L4 5'- GCGTTCCGGGATGCCTGAGGGACGGTCAGAATC-ATCATAAATCACCAGAACTGGCGCCTGCCCGGGTTTC -3'

O3L5 5'- CAGGCATCCCGGAACGCTTTAGCGGATCCAACA-GCGGCAACACCGCGACCCTGACCATTAGCGG -3'

O3L6 5'- CCGCTTCGTCTTCCGCCTGAGTGCCGCTAATGG-TCAGGGTC -3'

O1246H1 5'- GCTCTTCACCCCTGTTACCAAAGCCCAG-GTGCAATTG -3'

O1AH2 5'- GGCTTTGCAGCTCACTTTCACGCTGCTGCCCGG-TTTTTTCACTTCCGCGCCAGACTGAACCAATTGCACCTGGGC-TTTG -3'

Figure 6: (continued)

O1AH3 5'- GAAAGTGAGCTGCAAAGCCTCCGGAGGCACTTT-
TAGCAGCTATGCGATTAGCTGGGTGCGCCAAGCCCCTGGGCAG
GGTC -3'

O1AH4 5'- GCCCTGAAACTTCTGCGCGTAGTTCGCCGTGCC-
AAAAATCGGAATAATGCCGCCCATCCACTCGAGACCCTGCCC-
AGGGGC -3'

O1AH5 5'- GCGCAGAAGTTTCAGGGCCGGGTGACCATTACC-
GCGGATGAAAGCACCAGCACCGCGTATATGGAACTGAGCAGCC
TGCG -3'

O1ABH6 5'- GCGCGCAATAATACACGGCCGTATCTTCGCT-
ACGCAGGCTGCTCAGTTCC -3'

O1BH2 5'- GGCTTTGCAGCTCACTTTCACGCTCGCGCCCGG-
TTTTTTCACTTCCGCGCCGCTCTGAACCAATTGCACCTGGGC-
TTTG -3'

O1BH3 5'- GAAAGTGAGCTGCAAAGCCTCCGGATATACCTT-
TACCAGCTATTATATGCACTGGGTCCGCCAAGCCCCTGGGCAG
GGTC -3'

O1BH4 5'- GCCCTGAAACTTCTGCGCGTAGTTCGTGCCGCC-
GCTATTCGGGTTAATCCAGCCCATCCACTCGAGACCCTGCCCA
GGGGC -3'

O1BH5 5'- GCGCAGAAGTTTCAGGGCCGGGTGACCATGACC-
CGTGATACCAGCATTAGCACCGCGTATATGGAACTGAGCAGCC
TGCG -3'

O2H2 5'- GGTACAGGTCAGGGTCAGGGTTTGGGTCGGTTT-
CACCAGGGCCGGGCCGCTTTCTTTCAATTGCACCTGGGCTTTG
-3'

O2H3 5'- CTGACCCTGACCTGTACCTTTTCCGGATTTAGC-
CTGTCCACGTCTGGCGTTGGCGTGGGCTGGATTCGCCAGCCGC
CTGGGAAAG -3'

O2H4 5'- GCGTTTTCAGGCTGGTGCTATAATACTTATCAT-
CATCCCAATCAATCAGAGCCAGCCACTCGAGGGCTTTCCCAGG
CGGCTGG -3'

Figure 6: (continued)

O2H5 5'- GCACCAGCCTGAAAACGCGTCTGACCATTAGCA-AAGATACTTCGAAAAATCAGGTGGTGCTGACTATGACCAACATGG -3'

O2H6 5'- GCGCGCAATAATAGGTGGCCGTATCCACCGGGT-CCATGTTGGTCATAGTCAGC -3'

O3H1 5'- CGAAGTGCAATTGGTGGAAAGCGGCGGCGGCCT-GGTGCAACCGGGCGGCAG -3'

O3H2 5'- CATAGCTGCTAAAGGTAAATCCGGAGGCCGCGC-AGCTCAGACGCAGGCTGCCGCCCGGTTGCAC -3'

O3H3 5'- GATTTACCTTTAGCAGCTATGCGATGAGCTGGG-TGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTGAG -3'

O3H4 5'- GGCCTTTCACGCTATCCGCATAATAGGTGCTGC-CGCCGCTACCGCTAATCGCGCTCACCCACTCGAGACCC -3'

O3H5 5'- CGGATAGCGTGAAAGGCCGTTTTACCATTTCAC-GTGATAATTCGAAAAACACCCTGTATCTGCAAATGAACAG-3'

O3H6 5'- CACGCGCGCAATAATACACGGCCGTATCTTCCG-CACGCAGGCTGTTCATTTGCAGATACAGG -3'

O4H2 5'- GGTCAGGCTCAGGGTTTCGCTCGGTTTCACCAG-GCCCGGACCACTTTCTTGCAATTGCACCTGGGCTTTG -3'

O4H3 5'- GAAACCCTGAGCCTGACCTGCACCGTTTCCGGA-GGCAGCATTAGCAGCTATTATTGGAGCTGGATTCGCCAGCCGC -3'

O4H4 5'- GATTATAGTTGGTGCTGCCGCTATAATAAATAT-AGCCAATCCACTCGAGACCCTTCCCAGGCGGCTGGCGAATCCAG -3'

O4H5 5'- CGGCAGCACCAACTATAATCCGAGCCTGAAAAG-CCGGGTGACCATTAGCGTTGATACTTCGAAAAACCAGTTTAGCCTG -3'

O4H6 5'- GCGCGCAATAATACACGGCCGTATCCGCCGCCG-TCACGCTGCTCAGTTTCAGGCTAAACTGGTTTTTCG -3'

Figure 6: (continued)

O5H1 5'- GCTCTTCACCCCTGTTACCAAAGCCGAAGTGCA-ATTG -3'

O5H2 5'- CCTTTGCAGCTAATTTTCAGGCTTTCGCCCGGT-TTTTTCACTTCCGCGCCGCTCTGAACCAATTGCACTTCGGCTT TGG -3'

O5H3 5'- CCTGAAAATTAGCTGCAAAGGTTCCGGATATTC-CTTTACGAGCTATTGGATTGGCTGGGTGCGCCAGATGCCTGG -3'

O5H4 5'- CGGAGAATAACGGGTATCGCTATCGCCCGGATA-AATAATGCCCATCCACTCGAGACCCTTCCCAGGCATCTGGCGC AC -3'

O5H5 5'- CGATACCCGTTATTCTCCGAGCTTTCAGGGCCA-GGTGACCATTAGCGCGGATAAAAGCATTAGCACCGCGTATCTT C -3'

O5H6 5'- GCGCGCAATAATACATGGCCGTATCGCTCGCTT-TCAGGCTGCTCCATTGAAGATACGCGGTGCTAATG -3'

O6H2 5'- GAAATCGCACAGGTCAGGCTCAGGGTTTGGCTC-GGTTTCACCAGGCCCGGACCAGACTGTTGCAATTGCACCTGG-GCTTTG -3'

O6H3 5'- GCCTGACCTGTGCGATTTCCGGAGATAGCGTGA-GCAGCAACAGCGCGGCGTGGAACTGGATTCGCCAGTCTCCTGG GCG -3'

O6H4 5'- CACCGCATAATCGTTATACCATTTGCTACGATA-ATAGGTACGGCCCAGCCACTCGAGGCCACGCCCAGGAGACTG-GCG -3'

O6H5 5'- GGTATAACGATTATGCGGTGAGCGTGAAAAGCC-GGATTACCATCAACCCGGATACTTCGAAAAACCAGTTTAGCCT GC -3'

O6H6 5'- GCGCGCAATAATACACGGCCGTATCTTCCGGGG-TCACGCTGTTCAGTTGCAGGCTAAACTGGTTTTTC -3'

OCLK1 5'- GGCTGAAGACGTGGGCGTGTATTATTGCCAGCA-GCATTATACCACCCCGCCGACCTTTGGCCAGGGTAC -3'

Figure 6: (continued)

OCLK2 5'- GCGGAAAAATAAACACGCTCGGAGCAGCACCG-TACGTTTAATTTCAACTTTCGTACCCTGGCCAAAGGTC -3'

OCLK3 5'- GAGCGTGTTTATTTTTCCGCCGAGCGATGAACA-ACTGAAAAGCGGCACGGCGAGCGTGGTGTGCCTGCTG -3'

OCLK4 5'- CAGCGCGTTGTCTACTTTCCACTGAACTTTCGC-TTCACGCGGATAAAAGTTGTTCAGCAGGCACACCACGC -3'

OCLK5 5'- GAAAGTAGACAACGCGCTGCAAAGCGGCAACAG-CCAGGAAAGCGTGACCGAACAGGATAGCAAAGATAG -3'

OCLK6 5'- GTTTTTCATAATCCGCTTTGCTCAGGGTCAGGG-TGCTGCTCAGAGAATAGGTGCTATCTTTGCTATCCTGTTCG -3'

OCLK7 5'- GCAAAGCGGATTATGAAAAACATAAAGTGTATG-CGTGCGAAGTGACCCATCAAGGTCTGAGCAGCCCGGTG -3'

OCLK8 5'- GGCATGCTTATCAGGCCTCGCCACGATTAAAAG-ATTTAGTCACCGGGCTGCTCAGAC -3'

OCH1 5'- GGCGTCTAGAGGCCAAGGCACCCTGGTGACGGT-TAGCTCAGCGTCGAC -3'

OCH2 5'- GTGCTTTTGCTGCTCGGAGCCAGCGGAAACACG-CTTGGACCTTTGGTCGACGCTGAGCTAACC -3'

OCH3 5'- CTCCGAGCAGCAAAAGCACCAGCGGCGGCACGG-CTGCCCTGGGCTGCCTGGTTAAAGATTATTTCC -3'

OCH4 5'- CTGGTCAGCGCCCCGCTGTTCCAGCTCACGGTG-ACTGGTTCCGGGAAATAATCTTTAACCAGGCA -3'

OCH5 5'- AGCGGGGCGCTGACCAGCGGCGTGCATACCTTT-CCGGCGGTGCTGCAAAGCAGCGGCCTG -3'

OCH6 5'- GTGCCTAAGCTGCTGCTCGGCACGGTCACAACG-CTGCTCAGGCTATACAGGCCGCTGCTTTGCAG -3'

OCH7 5'- GAGCAGCAGCTTAGGCACTCAGACCTATATTTG-CAACGTGAACCATAAACCGAGCAACACC -3'

OCH8 5'- GCGCGAATTCGCTTTTCGGTTCCACTTTTTTAT-CCACTTTGGTGTTGCTCGGTTTATGG -3'

Figure 7A: sequence of the synthetic Cκ gene segment

```
        V  A   A  P  S   V  F  I   F  P  P  S   D  E  Q
 BsiWI
~~~~~~
CGTACGGTGG CTGCTCCGAG CGTGTTTATT TTTCCGCCGA GCGATGAACA
GCATGCCACC GACGAGGCTC GCACAAATAA AAAGGCGGCT CGCTACTTGT

  L  K  S   G  T  A  S   V  V  C   L  L  N   N  F  Y
ACTGAAAAGC GGCACGGCGA GCGTGGTGTG CCTGCTGAAC AACTTTTATC
TGACTTTTCG CCGTGCCGCT CGCACCACAC GGACGACTTG TTGAAAATAG

P  R  E  A   K  V  Q   W  K  V  D   N  A  L   Q  S  G
CGCGTGAAGC GAAAGTTCAG TGGAAAGTAG ACAACGCGCT GCAAAGCGGC
GCGCACTTCG CTTTCAAGTC ACCTTTCATC TGTTGCGCGA CGTTTCGCCG

 N  S  Q  E   S  V  T   E  Q  D   S  K  D  S   T  Y  S
AACAGCCAGG AAAGCGTGAC CGAACAGGAT AGCAAAGATA GCACCTATTC
TTGTCGGTCC TTTCGCACTG GCTTGTCCTA TCGTTTCTAT CGTGGATAAG

  L  S  S   T  L  T  L   S  K  A   D  Y  E   K  H  K
TCTGAGCAGC ACCCTGACCC TGAGCAAAGC GGATTATGAA AAACATAAAG
AGACTCGTCG TGGGACTGGG ACTCGTTTCG CCTAATACTT TTTGTATTTC
```

Figure 7A: sequence of the synthetic Cκ gene segment (continued)

```
V  Y  A  C   E  V  T   H  Q  G  L   S  S  P   V  T  K
TGTATGCGTG CGAAGTGACC CATCAAGGTC TGAGCAGCCC GGTGACTAAA
ACATACGCAC GCTTCACTGG GTAGTTCCAG ACTCGTCGGG CCACTGATTT

 S  F  N  R   G  E  A  *
                StuI        SphI
              ~~~~~~~~     ~~~~~~
TCTTTTAATC GTGGCGAGGC CTGATAAGCA TGC
AGAAAATTAG CACCGCTCCG GACTATTCGT ACG
```

Figure 7B: sequence of the synthetic CH1 gene segment

```
      A  S   T  K  G   P  S  V  F   P  L  A   P  S  S
 BlpI   SalI
~~~~~~~~~~~~~~~~
GCTCAGCGTC GACCAAAGGT CCAAGCGTGT TTCCGCTGGC TCCGAGCAGC
CGAGTCGCAG CTGGTTTCCA GGTTCGCACA AAGGCGACCG AGGCTCGTCG

 K  S  T  S   G  G  T   A  A  L   G  C  L  V   K  D  Y
AAAAGCACCA GCGGCGGCAC GGCTGCCCTG GGCTGCCTGG TTAAAGATTA
TTTTCGTGGT CGCCGCCGTG CCGACGGGAC CCGACGGACC AATTTCTAAT

  F  P  E   P  V  T  V   S  W  N   S  G  A   L  T  S
TTTCCCGGAA CCAGTCACCG TGAGCTGGAA CAGCGGGGCG CTGACCAGCG
AAAGGGCCTT GGTCAGTGGC ACTCGACCTT GTCGCCCCGC GACTGGTCGC

G  V  H  T   F  P  A   V  L  Q  S   S  G  L   Y  S  L
GCGTGCATAC CTTTCCGGCG GTGCTGCAAA GCAGCGGCCT GTATAGCCTG
CGCACGTATG GAAAGGCCGC CACGACGTTT CGTCGCCGGA CATATCGGAC

 S  S  V  V   T  V  P   S  S  S   L  G  T  Q   T  Y  I
AGCAGCGTTG TGACCGTGCC GAGCAGCAGC TTAGGCACTC AGACCTATAT
TCGTCGCAAC ACTGGCACGG CTCGTCGTCG AATCCGTGAG TCTGGATATA
```

Figure 7B: sequence of the synthetic CH1 gene segment (continued)

```
  C  N  V   N  H  K  P   S  N  T   K  V  D   K  K  V
TTGCAACGTG AACCATAAAC CGAGCAACAC CAAAGTGGAT AAAAAAGTGG
AACGTTGCAC TTGGTATTTG GCTCGTTGTG GTTTCACCTA TTTTTTCACC

E  P  K  S   E  F  *
             EcoRI     HindIII
            ~~~~~~     ~~~~~~
AACCGAAAAG CGAATTCTGA TAAGCTT
TTGGCTTTTC GCTTAAGACT ATTCGAA
```

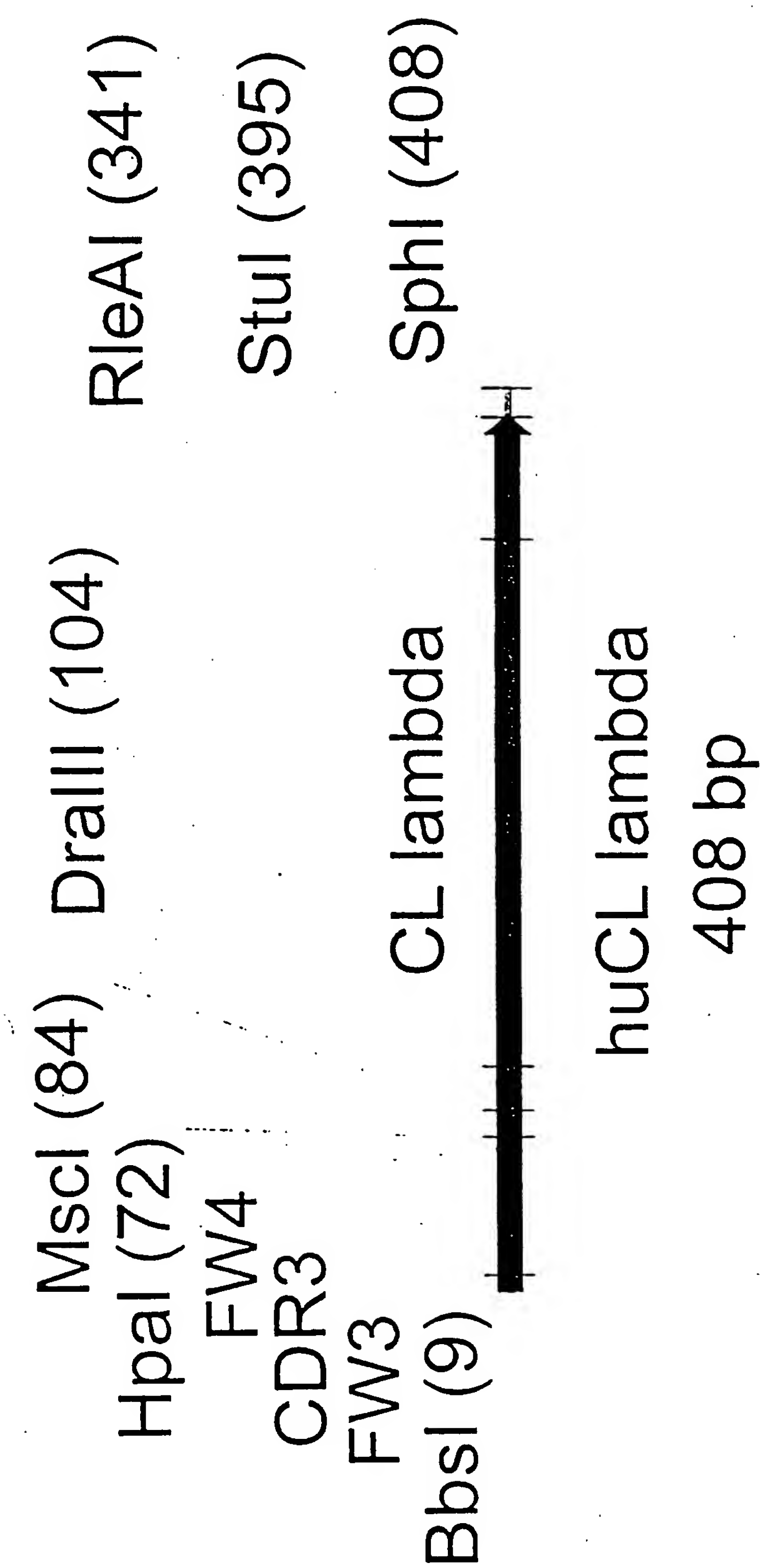


Figure 7C: functional map and sequence of module 24 comprising the synthetic Cλ gene segment (huCL lambda)

Figure 7C: functional map and sequence of module 24 comprising the synthetic CI gene segment (huCL lambda) (continued)

```
       BbsI
       ~~~~~~~
  1    GAAGACGAAG CGGATTATTA TTGCCAGCAG CATTATACCA CCCCGCCTGT
       CTTCTGCTTC GCCTAATAAT AACGGTCGTC GTAATATGGT GGGGCGGACA

                            HpaI       MscI          DraIII
                          ~~~~~~~~   ~~~~~~~            ~~~
 51    GTTTGGCGGC GGCACGAAGT TAACCGTTCT TGGCCAGCCG AAAGCCGCAC
       CAAACCGCCG CCGTGCTTCA ATTGGCAAGA ACCGGTCGGC TTTCGGCGTG

       DraIII
       ~~~~~~
101    CGAGTGTGAC GCTGTTTCCG CCGAGCAGCG AAGAATTGCA GGCGAACAAA
       GCTCACACTG CGACAAAGGC GGCTCGTCGC TTCTTAACGT CCGCTTGTTT

151    GCGACCCTGG TGTGCCTGAT TAGCGACTTT TATCCGGGAG CCGTGACAGT
       CGCTGGGACC ACACGGACTA ATCGCTGAAA ATAGGCCCTC GGCACTGTCA

201    GGCCTGGAAG GCAGATAGCA GCCCCGTCAA GGCGGGAGTG GAGACCACCA
       CCGGACCTTC CGTCTATCGT CGGGGCAGTT CCGCCCTCAC CTCTGGTGGT
```

Figure 7C: functional map and sequence of module 24 comprising the synthetic Cl gene segment (huCL lambda) (continued)

```
251   CACCCTCCAA ACAAAGCAAC AACAAGTACG CGGCCAGCAG CTATCTGAGC
      GTGGGAGGTT TGTTTCGTTG TTGTTCATGC GCCGGTCGTC GATAGACTCG

                                  RleAI
                                ~~~~~~~
301   CTGACGCCTG AGCAGTGGAA GTCCCACAGA AGCTACAGCT GCCAGGTCAC
      GACTGCGGAC TCGTCACCTT CAGGGTGTCT TCGATGTCGA CGGTCCAGTG

                                                   StuI
                                                 ~~~~~~~
351   GCATGAGGGG AGCACCGTGG AAAAAACCGT TGCGCCGACT GAGGCCTGAT
      CGTACTCCCC TCGTGGCACC TTTTTTGGCA ACGCGGCTGA CTCCGGACTA

        SphI
       ~~~~~
401   AAGCATGC
      TTCGTACG
```

Figure 7D: oligonucleotides used for synthesis of module M24 containing Cλ gene segment

M24: assembly PCR

M24-A: GAAGACAAGCGGATTATTATTGCCAGCAGCATTATACCACCCCGCCTGTGTTTGGCGGCG-GCACGAAGTTAACCGTTC

M24-B: CAATTCTTCGCTGCTCGGCGGAAACAGCGTCACACTCGGTGCGGCTTTCGGCTGGCCAA-GAACGGTTAACTTCGTGCCGC

M24-C: CGCCGAGCAGCGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGCCTGATTAGCGACT-TTTATCCGGGAGCCGTGACA

M24-D: TGTTTGGAGGGTGTGGTGGTCTCCACTCCCGCCTTGACGGGGCTGCTATCTGCCTTCCAG-GCCACTGTCACGGCTCCCGG

M24-E: CCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGC-CTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTG

M24-F: GCATGCTTATCAGGCCTCAGTCGGCGCAACGGTTTTTTCCACGGTGCTCCCCTCATGCGT-GACCTGGCAGCTGTAGCTTC

Figure 8: sequence and restriction map of the synthetic gene encoding the consensus single-chain fragment VH3-Vκ2

```
 M  K  Q  S   T  I  A   L  A  L   L  P  L  L   F  T  P
                                         SapI
                                       ~~~~~~~~~
ATGAAACAAA GCACTATTGC ACTGGCACTC TTACCGTTGC TCTTCACCCC
TACTTTGTTT CGTGATAACG TGACCGTGAG AATGGCAACG AGAAGTGGGG

  V  T  K   A  D  Y  K   D  E  V   Q  L  V   E  S  G
                                  MfeI
                                 ~~~~~~~
TGTTACCAAA GCCGACTACA AAGATGAAGT GCAATTGGTG GAAAGCGGCG
ACAATGGTTT CGGCTGATGT TTCTACTTCA CGTTAACCAC CTTTCGCCGC

G  G  L  V   Q  P  G   G  S  L  R   L  S  C   A  A  S
                                                 BspEI
                                                   ~~~
GCGGCCTGGT GCAACCGGGC GGCAGCCTGC GTCTGAGCTG CGCGGCCTCC
CGCCGGACCA CGTTGGCCCG CCGTCGGACG CAGACTCGAC GCGCCGGAGG

 G  F  T  F   S  S  Y   A  M  S   W  V  R  Q   A  P  G
BspEI                                        BstXI
~~~                                        ~~~~~~~~~~~~~~
GGATTTACCT TTAGCAGCTA TGCGATGAGC TGGGTGCGCC AAGCCCCTGG

CCTAAATGGA AATCGTCGAT ACGCTACTCG ACCCACGCGG TTCGGGGACC
```

Figure 8: sequence and restriction map of the synthetic gene encoding the consensus single-chain fragment VH3-Vκ2 (continued)

```
  K  G  L  E  W  V  S  A  I  S  G  S  G  G  S  T
         XhoI
        ~~~~~~~~
GAAGGGTCTC GAGTGGGTGA GCGCGATTAG CGGTAGCGGC GGCAGCACCT
CTTCCCAGAG CTCACCCACT CGCGCTAATC GCCATCGCCG CCGTCGTGGA

 Y  Y  A  D  S  V  K  G  R  F  T  I  S  R  D  N  S
                                      PmlI       NspV
                                    ~~~~~~~~     ~~~~
ATTATGCGGA TAGCGTGAAA GGCCGTTTTA CCATTTCACG TGATAATTCG
TAATACGCCT ATCGCACTTT CCGGCAAAAT GGTAAAGTGC ACTATTAAGC

  K  N  T  L  Y  L  Q  M  N  S  L  R  A  E  D  T  A
NspV                                              EagI
~~                                                ~~~~
AAAAACACCC TGTATCTGCA AATGAACAGC CTGCGTGCGG AAGATACGGC
TTTTTGTGGG ACATAGACGT TTACTTGTCG GACGCACGCC TTCTATGCCG

  V  Y  Y  C  A  R  W  G  G  D  G  F  Y  A  M  D
EagI        BssHII
~~          ~~~~~~~
CGTGTATTAT TGCGCGCGTT GGGGCGGCGA TGGCTTTTAT GCGATGGATT
```

Figure 8: sequence and restriction map of the synthetic gene encoding the consensus single-chain fragment VH3-Vκ2 (continued)

```
GCACATAATA ACGCGCGCAA CCCCGCCGCT ACCGAAAATA CGCTACCTAA
Y   W   G   Q    G   T   L    V   T   V   S    S   A   G    G   G   S
          StyI                            BlpI
         ~~~~~~~~                        ~~~~~~~~
ATTGGGGCCA AGGCACCCTG GTGACGGTTA GCTCAGCGGG TGGCGGTTCT
TAACCCCGGT TCCGTGGGAC CACTGCCAAT CGAGTCGCCC ACCGCCAAGA

 G   G   G   G    S   G   G    G   G   S    G   G   G   G    S   D   I
                                                              EcoRV
                                                              ~~~~~
GGCGGCGGTG GGAGCGGTGG CGGTGGTTCT GGCGGTGGTG GTTCCGATAT
CCGCCGCCAC CCTCGCCACC GCCACCAAGA CCGCCACCAC CAAGGCTATA

  V   M   T    Q   S   P   L    S   L   P    V   T   P    G   E   P
EcoRV              BanII
~                 ~~~~~~~
CGTGATGACC CAGAGCCCAC TGAGCCTGCC AGTGACTCCG GGCGAGCCTG
GCACTACTGG GTCTCGGGTG ACTCGGACGG TCACTGAGGC CCGCTCGGAC

A   S   I   S    C   R   S    S   Q   S   L    L   H   S    N   G   Y
                PstI
               ~~~~~~~
CGAGCATTAG CTGCAGAAGC AGCCAAAGCC TGCTGCATAG CAACGGCTAT
GCTCGTAATC GACGTCTTCG TCGGTTTCGG ACGACGTATC GTTGCCGATA
```

Figure 8: sequence and restriction map of the synthetic gene encoding the consensus single-chain fragment VH3-Vκ2 (continued)

```
 N  Y  L  D   W  Y  L   Q  K  P   G  Q  S  P   Q  L  L
               KpnI          SexAI              AseI
              -------       ---------           ---
AACTATCTGG ATTGGTACCT TCAAAAACCA GGTCAAAGCC CGCAGCTATT
TTGATAGACC TAACCATGGA AGTTTTTGGT CCAGTTTCGG GCGTCGATAA

  I  Y  L   G  S  N  R   A  S  G   V  P  D   R  F  S
AseI                          Eco0109I
---                          ---------
AATTTATCTG GGCAGCAACC GTGCCAGTGG GGTCCCGGAT CGTTTTAGCG
TTAAATAGAC CCGTCGTTGG CACGGTCACC CCAGGGCCTA GCAAAATCGC

G  S  G  S   G  T  D   F  T  L  K   I  S  R   V  E  A
       BamHI
      --------
GCTCTGGATC CGGCACCGAT TTTACCCTGA AAATTAGCCG TGTGGAAGCT
CGAGACCTAG GCCGTGGCTA AAATGGGACT TTTAATCGGC ACACCTTCGA

 E  D  V  G   V  Y  Y   C  Q  Q   H  Y  T  T   P  P  T
 BbsI
-------
GAAGACGTGG GCGTGTATTA TTGCCAGCAG CATTATACCA CCCCGCCGAC
CTTCTGCACC CGCACATAAT AACGGTCGTC GTAATATGGT GGGGCGGCTG
```

Figure 8: sequence and restriction map of the synthetic gene encoding the consensus single-chain fragment VH3-Vκ2 (continued)

```
  F  G  Q    G  T  K  V    E  I  K    R  T  E    F
    MscI                              BsiWI EcoRI
   ~~~~~~~                           ~~~~~~~~~~~~~
CTTTGGCCAG GGTACGAAAG TTGAAATTAA ACGTACGGAA TTC
GAAACCGGTC CCATGCTTTC AACTTTAATT TGCATGCCTT AAG
```

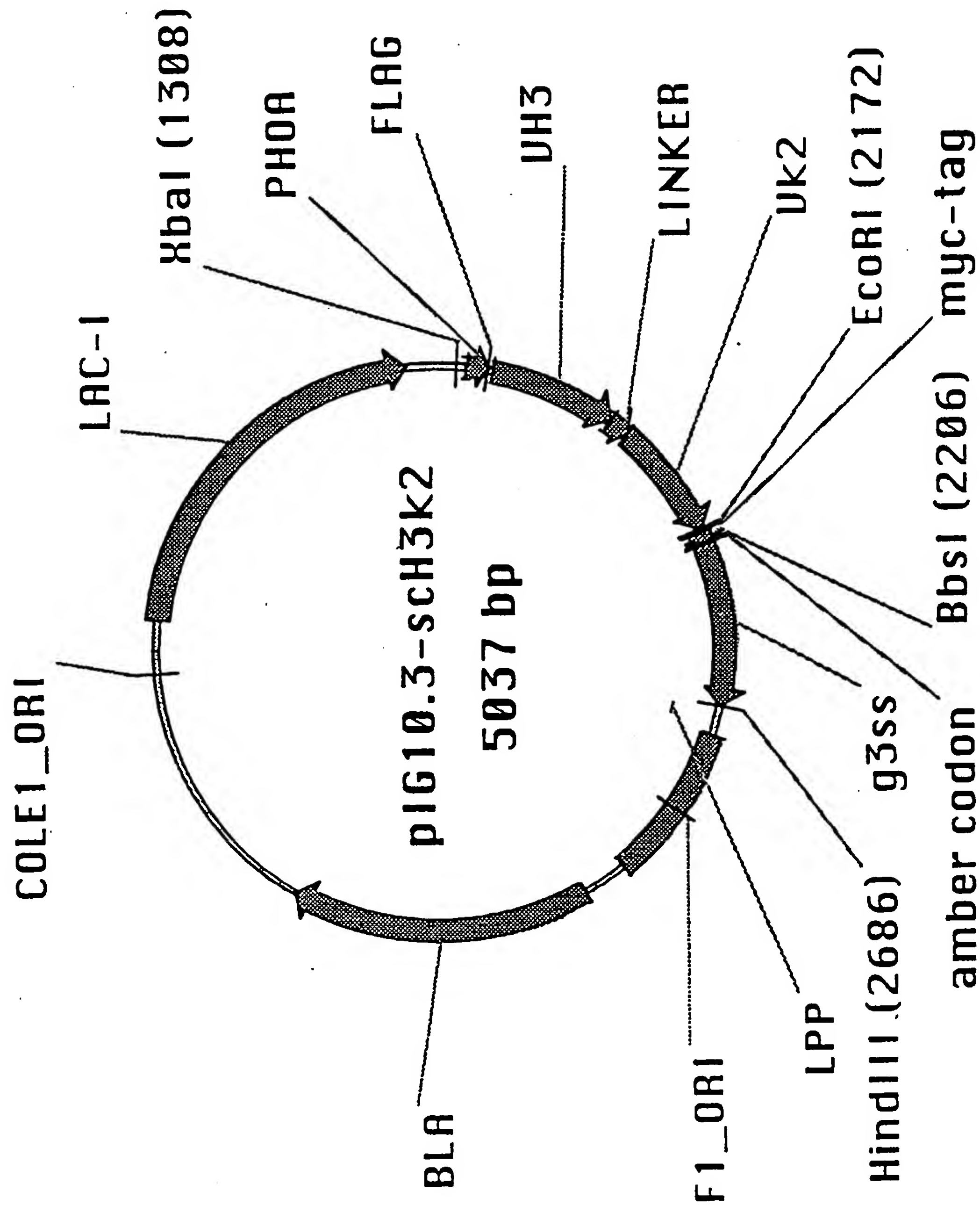


Figure 9: Phage display vector pIG10.3

Figure 10: Sequence analysis of initial libraries

	92	93	94	95	96	97	98	99	100	100A	100B	100C	100D	100E	101	102	103
A	C	A	R	W	G	G	D	G	F	Y	A	-	-	M	D	Y	W
B	C	A	R	F	G	K	M	N	Y	-	-	-	-	-	D	Y	W
	C	A	R	H	R	T	E	W	H	-	-	-	-	-	D	Y	W
	C	A	R	V	R	E	L	Y	H	-	-	-	-	-	D	Y	W
	C	A	R	K	F	L	K	A	R	-	-	-	-	-	D	Y	W
	C	A	R	W	N	T	T	G	Y	-	-	-	-	-	D	Y	W
	C	A	R	I	N	E	A	Q	P	-	-	-	-	-	D	Y	W
	C	A	R	T	A	I	T	R	-	-	-	-	-	-	D	Y	W
	C	A	R	W	Y	N	R	N	S	-	-	-	-	-	D	Y	W
	C	A	R	S	V	G	D	S	K	-	-	-	-	-	D	Y	W
	C	A	R	S	K	T	F	A	A	-	-	-	-	-	D	Y	W
	C	A	R	V	A	P	Q	Y	D	-	-	-	-	-	D	Y	W
	C	A	R	M	Q	S	E	W	M	-	-	-	-	-	D	Y	W

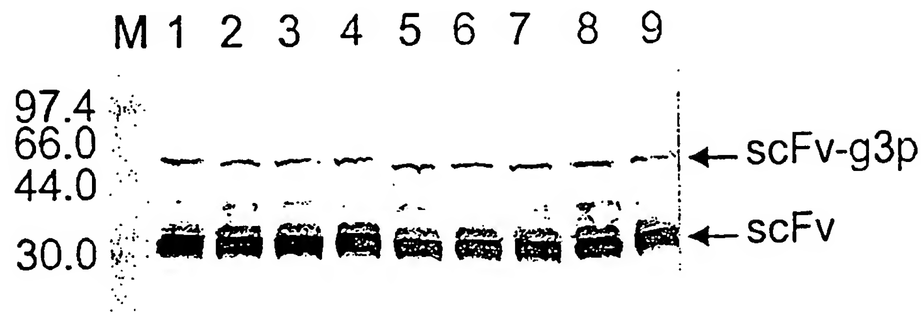
Figure 10: Sequence analysis of initial libraries

C

C	A	R	Y	F	V	H	F	L	Y	T	M	V	M	D	V	W
C	A	R	M	A	L	R	A	S	G	K	Y	I	M	D	V	W
C	A	R	K	N	Q	M	V	F	H	A	R	K	F	D	V	W
C	A	R	T	Q	S	F	W	E	Q	Q	K	V	M	D	Y	W
C	A	R	Y	P	Y	R	S	N	F	F	M	P	M	D	V	W
C	A	R	*	G	S	G	S	E	H	W	S	I	F	D	V	W
C	A	R	R	N	P	W	N	V	N	Y	L	H	F	D	V	W
C	A	R	M	K	P	M	L	N	R	D	G	T	M	D	V	W
C	A	R	K	G	S	E	F	L	E	T	D	V	M	D	Y	W
C	A	R	S	W	T	N	D	K	P	N	F	I	M	D	V	W
C	A	R	Y	A	G	T	T	F	K	Q	G	P	M	D	Y	W

Figure 11: Expression analysis of initial library

A



B

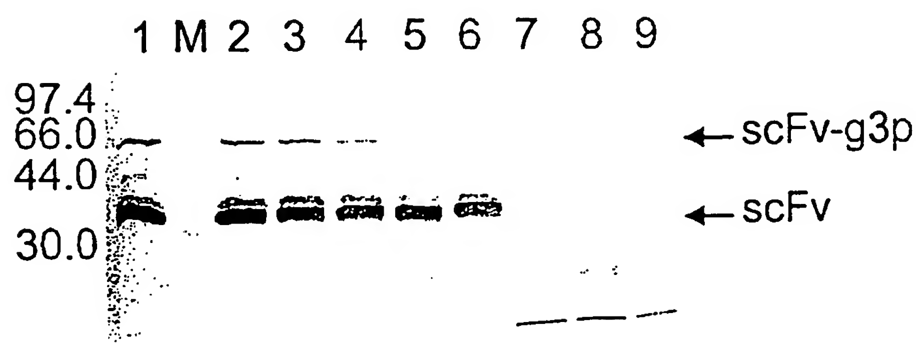


Figure 12: Increase of specificity during the panning rounds

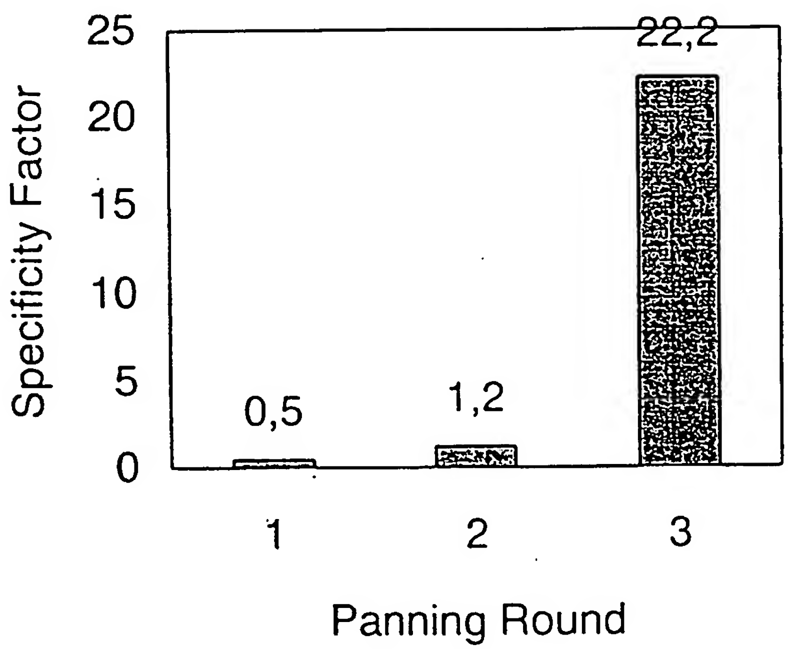


Figure 13: Phage ELISA of clones after the 3rd round of panning

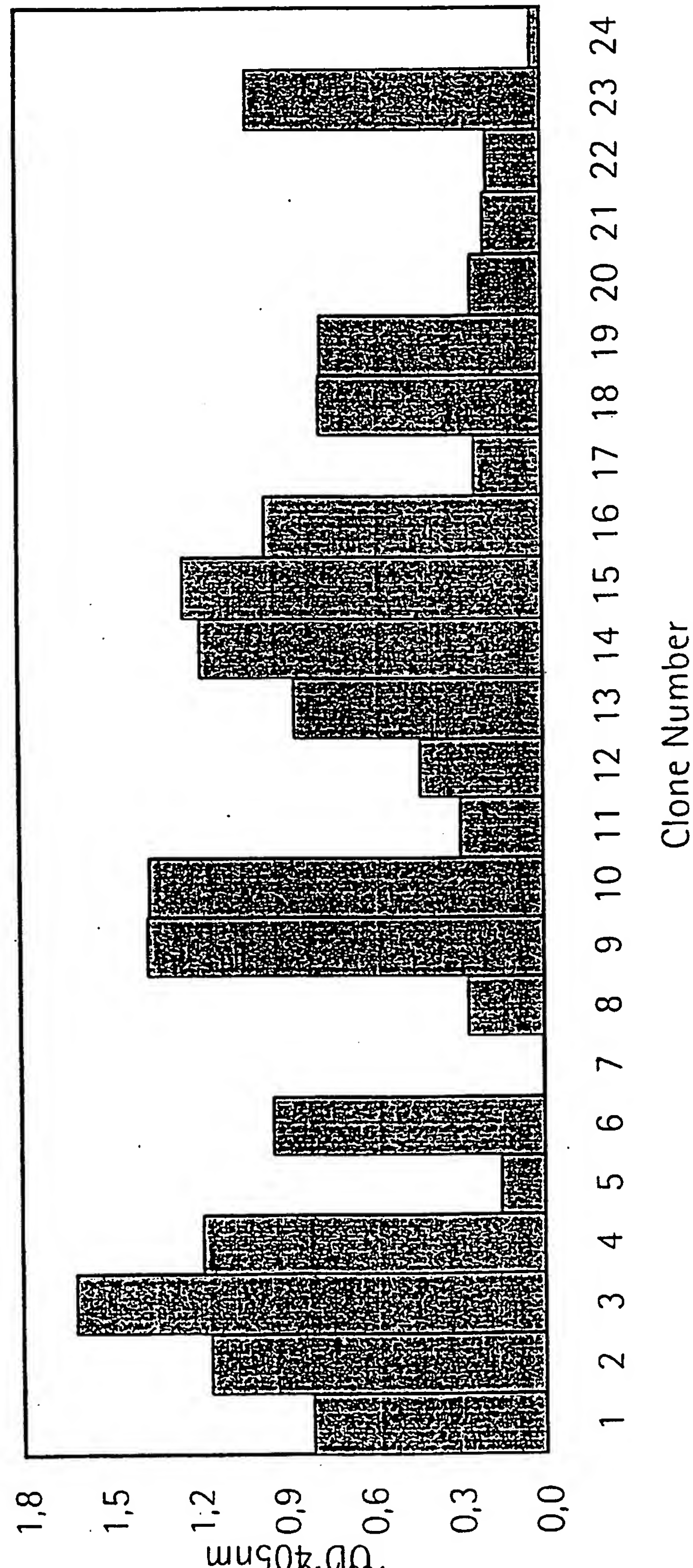


Figure 14: Competition ELISA

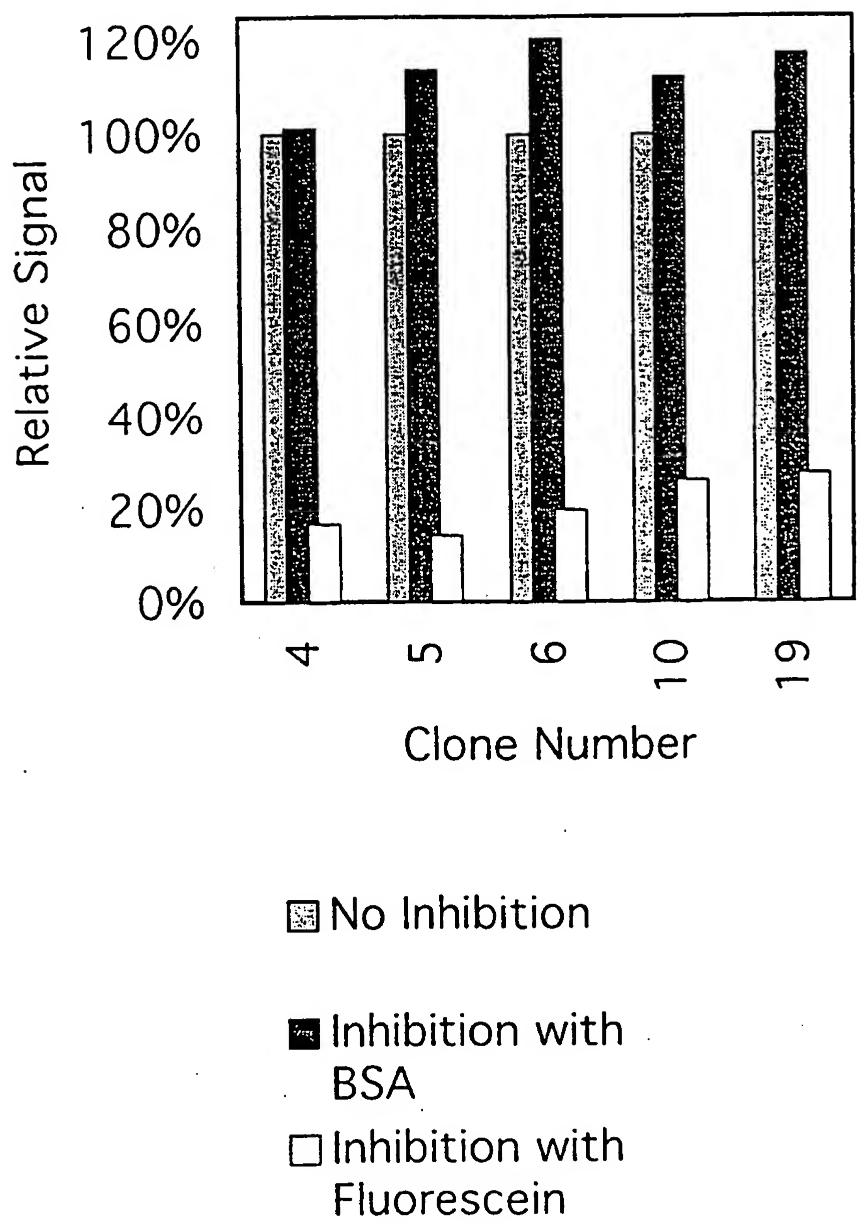


Figure 15: Sequence analysis of fluorescein binders

92	93	94	95	96	97	98	99	100	100A	100B	100C	100D	100E	101	102	103	Frequency
C	A	R	K	R	M	M	Q	N	P	R	F	R	F	D	V	W	1
C	A	R	R	S	K	Q	K	R	K	M	R	R	F	D	V	W	3
C	A	R	R	N	G	K	R	H	L	R	H	R	F	D	V	W	1
C	A	R	R	K	M	R	K	R	I	K	R	R	F	D	V	W	2
C	A	R	Y	R	K	I	M	K	W	K	N	S	F	D	V	W	1
C	A	R	L	I	E	V	H	P	S	F	D	Q	M	D	V	W	1
C	A	R	R	K	P	M	F	L	K	K	A	V	F	D	V	W	1
C	A	R	R	K	F	H	R	Y	S	T	V	K	F	D	Y	W	2
C	A	R	R	K	T	M	R	S	R	V	K	Y	F	D	Y	W	1
C	A	R	K	K	R	S	W	R	R	M	D	R	F	D	V	W	1
C	A	R	R	N	P	R	R	G	R	M	N	R	F	D	V	W	1
C	A	R	K	G	K	K	K	F	A	R	P	R	F	D	V	W	1
C	A	R	R	M	V	H	K	G	K	R	K	I	F	D	V	W	1
C	A	R	R	K	H	I	T	Y	P	R	K	Q	F	D	V	W	1
C	A	R	R	W	T	K	R	R	S	F	A	R	F	D	V	W	1
C	A	R	K	K	L	K	Q	Y	T	F	S	R	F	D	Y	W	1

Figure 16: Purification of fluorescein binding scFv fragments

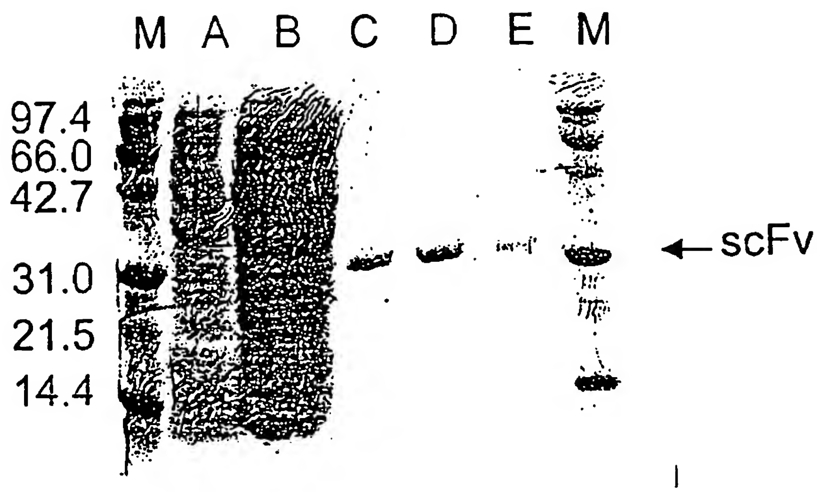


Figure 17: Enrichment factors after three rounds of panning

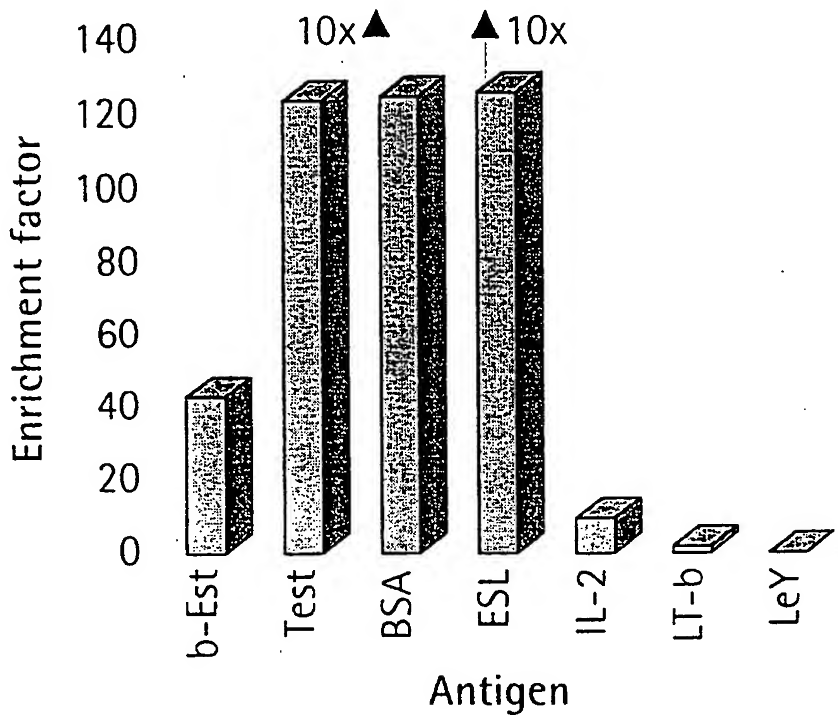


Figure 18: ELISA of anti-ESL-1 and anti-β-estradiol antibodies

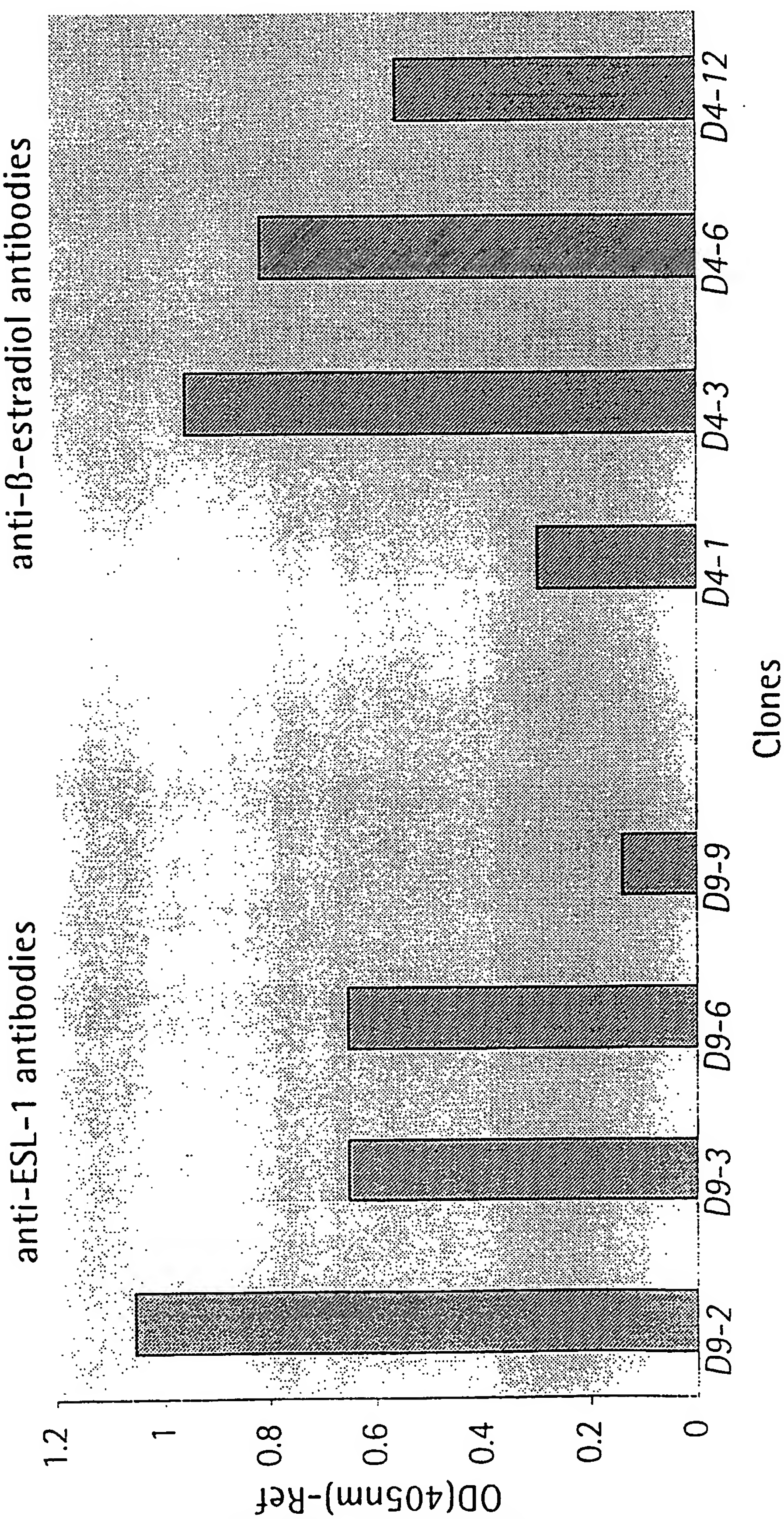


Figure 19: Selectivity and cross-reactivity of HuCAL antibodies

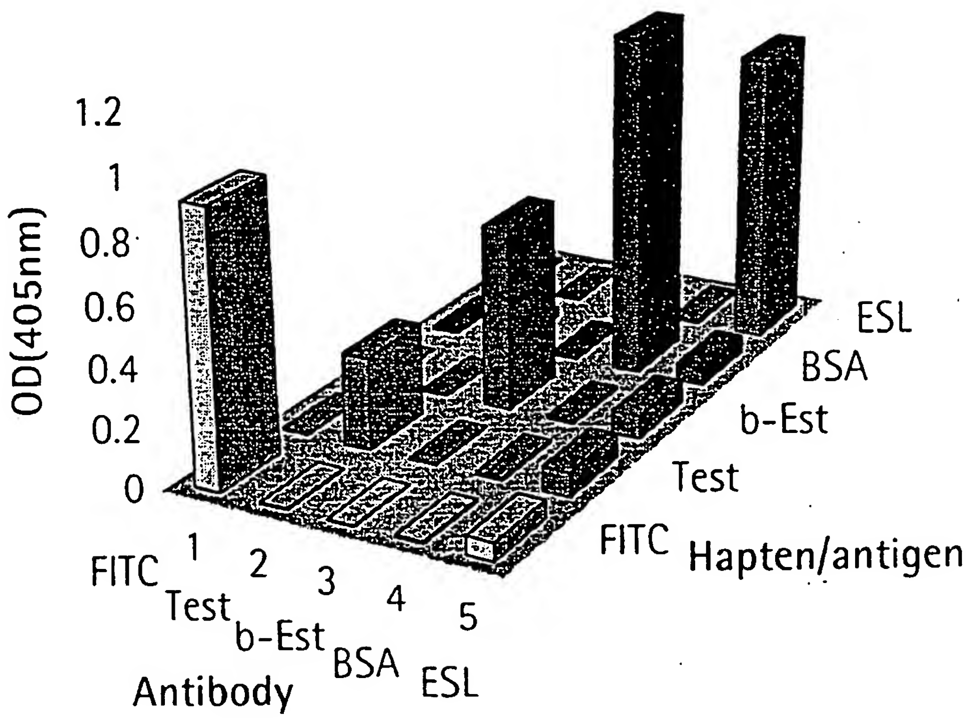


Figure 20: Sequence analysis of estradiol binders

92	93	94	95	96	97	98	99	100	100A	100B	100C	100D	100E	101	102	103	Frequency
C	A	R	T	R	P	W	Q	A	T	R	K	G	F	D	V	W	3
C	A	R	N	Q	W	E	F	K	N	R	R	K	M	D	Y	W	8
C	A	R	K	R	W	M	W	P	I	G	K	R	F	D	Y	W	7
C	A	R	Y	S	L	W	R	L	D	E	Y	F	F	D	Y	W	1
C	A	R	V	P	W	G	D	F	W	S	W	H	M	D	V	W	1
C	A	R	N	G	L	E	P	R	H	R	K	M	M	D	Y	W	1
C	A	R	I	M	K	A	P	P	-	-	-	-	-	D	Y	W	1
C	A	R	R	K	T	W	H	W	F	Y	K	R	M	D	Y	W	1
C	A	R	W	K	D	M	W	S	Q	V	Y	V	M	D	Y	W	1
C	A	R	N	K	Q	Q	M	R	F	R	R	F	M	D	Y	W	5
C	A	R	N	M	L	A	L	S	R	G	K	E	M	D	V	W	4
C	A	R	N	M	R	L	M	R	M	R	K	N	F	D	V	W	1

Figure 21: Sequence analysis of testosterone binders

92	93	94	95	96	97	98	99	100	100A	100B	100C	100D	100E	101	102	103	Frequency
C	A	R	Y	I	K	Q	A	K	R	K	L	A	F	D	Y	W	4
C	A	R	Y	N	R	H	A	W	Q	K	M	Q	F	D	Y	W	3
C	A	R	Y	V	K	Y	A	R	N	K	M	Q	F	D	Y	W	2
C	A	R	Y	K	R	G	A	W	M	K	T	M	F	D	V	W	1
C	A	R	R	K	P	L	R	R	I	M	K	W	F	D	Y	W	1
C	A	R	Y	R	K	R	A	S	R	Q	M	Q	F	D	Y	W	1

Figure 22: Sequence analysis of lymphotoxin-ß binders

92	93	94	95	96	97	98	99	100	100A	100B	100C	100D	100E	101	102	103	Frequency
C	A	R	Q	R	Y	R	S	K	I	K	G	H	F	D	V	W	16
C	A	R	_	W	R	D	F	N	S	Y	D	P	M	D	Y	W	1
C	A	R	M	A	D	L	D	N	Y	W	V	Q	F	D	Y	W	1
C	A	R	L	Q	A	Y	L	K	P	H	H	W	M	D	Y	W	1
C	A	R	R	L	I	E	Q	A	R	D	H	V	M	D	Y	W	1
C	A	R	S	W	H	N	S	Q	F	T	Q	S	F	D	V	W	1
C	A	R	V	D	H	F	Q	T	E	N	E	W	M	D	Y	W	1
C	A	R	D	W	P	T	L	I	F	W	Y	W	F	D	Y	W	1

Figure 23: Sequence analysis of ESL-1 binders

92	93	94	95	96	97	98	99	100	100A	100B	100C	100Ca	100D	100E	101	102	103	Frequency
C	A	R	G	F	G	F	T	E	-	-	-	-	-	-	D	Y	W	4
C	A	R	Q	F	D	E	D	S	F	V	R	-	R	F	D	V	W	4
C	A	R	I	L	K	E	S	S	K	S	R	-	Q	M	D	V	W	2
C	A	R	E	Q	D	E	Y	G	A	I	R	-	I	M	D	Y	W	1
C	A	R	N	H	F	E	A	S	W	P	R	R	Q	M	D	V	W	1
C	A	R	E	N	E	W	V	D	M	I	L	-	D	M	D	Y	W	2
C	A	R	Q	Y	S	E	T	R	W	V	R	-	K	F	D	Y	W	1
C	A	R	Q	F	K	E	S	K	T	R	R	-	K	F	D	V	W	13
C	A	R	K	K	T	Q	Y	V	H	D	W	-	R	M	D	V	W	3
C	A	R	R	W	R	E	T	K	S	K	R	-	F	F	D	V	W	1
C	A	R	D	Y	I	M	E	F	-	-	-	-	-	-	D	Y	W	1
C	A	R	Q	F	E	E	T	K	Q	R	R	-	L	M	D	Y	W	1

SUBSTITUTE SHEET (RULE 26)

Figure 24: Sequence analysis of BSA binders

92	93	94	95	96	97	98	99	100	100A	100B	100C	100D	100E	101	102	103	*Frequency*
C	A	R	D	Q	G	F	Y	A	I	D	Y	V	M	D	Y	W	5
C	A	R	V	F	T	Y	M	Y	N	Y	F	R	F	D	V	W	1
C	A	R	V	F	F	E	Q	M	E	V	V	R	M	D	V	W	1
C	A	R	E	K	E	Y	R	L	S	W	S	Q	M	D	Y	W	1
C	A	R	Y	P	S	R	W	A	P	N	W	Y	M	D	Y	W	1
C	A	R	D	G	G	F	K	P	L	T	H	F	F	D	V	W	1

Figure 25: modular pCAL vector system

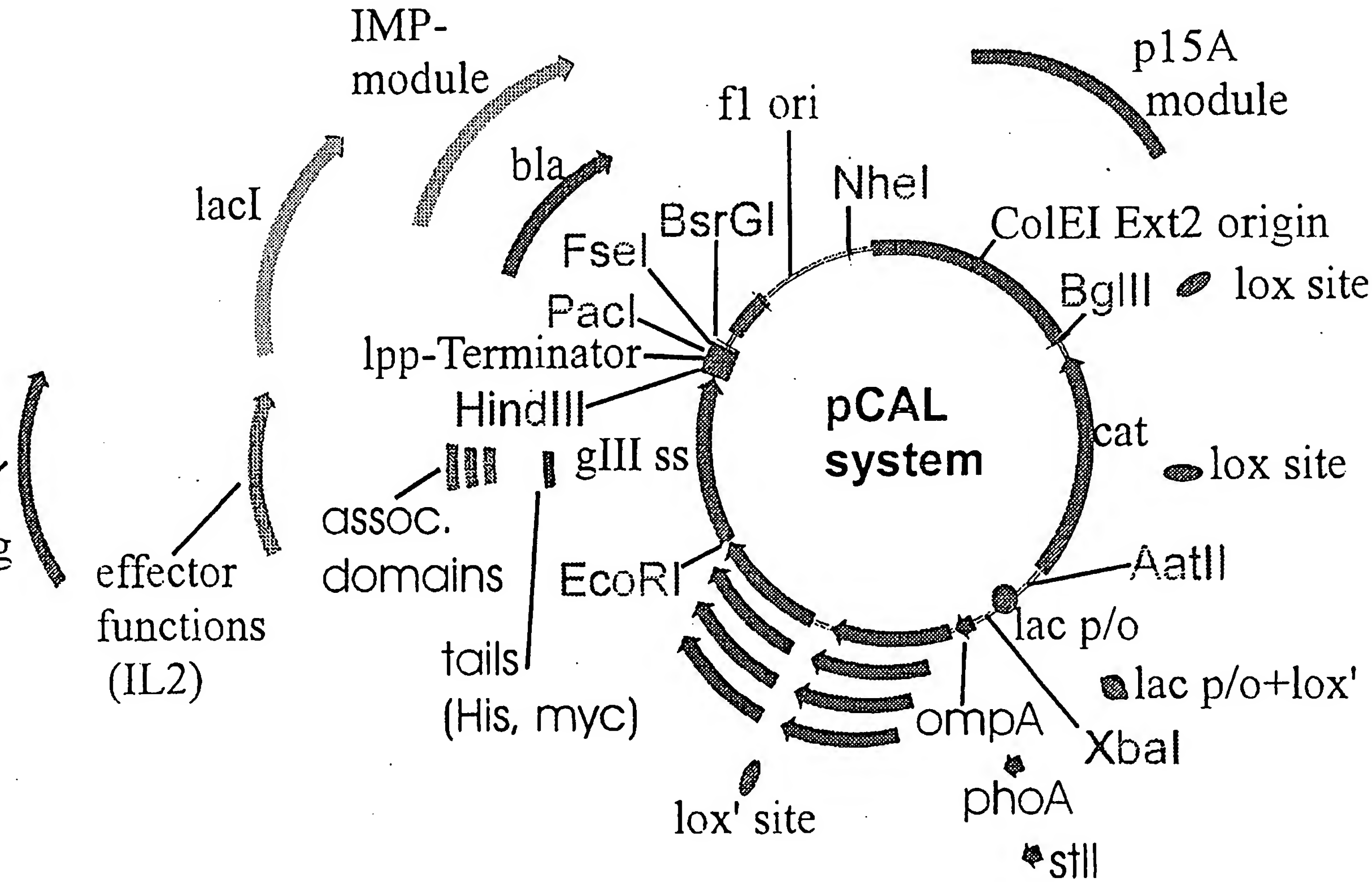


Figure 25a: List of unique restriction sites used in or suitable for HuCAL genes or pCAL vectors

unique restriction site	Isoschizomers
AatII	/
AflII	BfrI, BspTI, Bst98I
AscI	/
AseI	VspI, AsnI, PshBI
BamHI	BstI
BbeI	EheI, KasI, NarI
BbsI	BpuAI, BpiI
BglII	/
BlpI	Bpu1102I,CelII, BlpI
BsaBI	MamI, Bsh1365I, BsrBRI
BsiWI	Pfl23II, SplI, SunI
BspEI	AccIII, BseAI, BsiMI, Kpn2I, MroI
BsrGI	Bsp1407I, SspBI
BssHII	PauI
BstEII	BstPI, Eco91I, Eco0651
BstXI	/
Bsu36I	AocI, CvnI, Eco81I
DraIII	/
DsmAI	
EagI	BstZI, EclXI, Eco52I, XmaIII
Eco57I	/
Eco0109I	DraII
EcoRI	/
EcoRV	Eco32I
FseI	/
HindIII	/
HpaI	/
KpnI	Acc65I, Asp718I
MluI	/
MscI	BalI, MluNI

Figure 25a: List of unique restriction sites used in or suitable for HuCAL genes or pCAL vectors

unique restriction site	Isoschizomers
MunI	MfeI
NheI	/
NsiI	Ppu10I, EcoT22I, Mph1103I
NspV	Bsp119I, BstBI, Csp45I, LspI, SfuI
PacI	/
PmeI	/
PmlI	BbrPI, Eco72I, PmaCI
Psp5II	PpuMI
PstI	/
RsrII	(RsriI), CpoI, CspI
SanDI	/
SapI	/
SexAI	/
SpeI	/
SfiI	/
SphI	BbuI, PaeI,NspI
StuI	AatI, Eco147I
StyI	Eco130I, EcoT14I
XbaI	BspLU11II
XhoI	PaeR7I
XmaI	AvaI, SmaI, Cfr9I, PspAI

Figure26: list of pCAL vector modules

No	module/flanking restriction sites	functional element	sites to be removed	sites to be inserted	template	reference
M1	AatII-lacp/o-XbaI	lac promotor/operator	2x VspI (AseI)	AatII	vector pASK30	Skerra et al. (1991) Bio/Technology 9, 273-278
M2	BglII-lox-AatII	Cre/lox recombination site	2x VspI (AseI)	lox, BglII	(synthetic)	Hoess et al. (1986) Nucleic Acids Res. 2287-2300
M3	XbaI-lox'-SphI	Cre/lox' recombination site	none	lox', SphI	(synthetic)	see M2
M7-I	EcoRI-gIIIlong-HindIII	gIIIp of filamentous phage with N-terminal myctail/amber codon	SphI, BamHI	none	vector pIG10	Ge et al., (1994) Expressing antibodies in E. coli. In: Antibody engineering: A practical approach. IRL Press, New York, pp 229-266

Figure26: list of pCAL vector modules

M7-II	EcoRI-gIIIss-HindIII	truncated gIIIp of filamentous phage with N-terminal Gly-Ser linker	SphI		vector pIG10	see M7-I
M7-III	EcoRI-gIIIss-HindIII	truncated gIIIp of filamentous phage with N-terminal myctail/amber codon	SphI, BbsI		vector pIG10	see M7-I
M8	SphI-lox-HindIII	Cre/lox recombination site	none	lox	(synthetic)	see M3
M9-II	HindIII-lpp-PacI	lpp-terminator	none	PacI, FseI	(synthetic)	see M1
M10-II	PacI/FseI-bla-BsrGI	beta-lactamase/bla (ampR)	VspI, Eco57I, BssSI	PacI, FseI, BsrGI	pASK30	see M1
M11-II	BsrGI-f1 ori-NheI	origin of single-stranded replication	DraIII (BanII not removed)	BsrGI, NheI	pASK30	see M1
M11-III	BsrGI-f1 ori-NheI	origin of single-stranded replication	DraIII, BanII	BsrGI, NheI	pASK30	see M1

Figure26: list of pCAL vector modules

M12	NheI-p15A-BglII	origin of double-stranded replication	BssSI, VspI, NspV	NheI, BglII	pACYC184	Rose, R.E. (1988) Nucleic Acids Res. 16, 355
M13	BglII-lox-BglII	Cre/lox recombination site	none	BglII, lox, XmnI	(synthetic)	see M3
M14-Ext2	BglII-ColEI-NheI	origin of double-stranded replication	Eco57I (BssSI not removed)	BglII, NheI	pUC19	Yanisch-Peron, C. (1985) Gene 33,103-119
M17	AatII-cat-BglII	chloramphenicol-acetyltransferase/ cat (camR)	BspEI, MscI, StyI/NcoI		pACYC184	Cardoso, M. & Schwarz,S. (1992) J. Appl. Bacteriol.72, 289-293
M19	XbaI-phoA-EcoRI	signal sequence of phosphatase A	(synthetic)		(synthetic)	see M1
M20	XbaI-phoA-FLAG-EcoRI	signal sequence of phosphatase A + FLAG detection tag	(synthetic)		(synthetic)	Knappik, A & Plückthun, A. (1994) BioTechniques 17, 754-761

Figure26: list of pCAL vector modules

M21	Xbal-stII-Sapl	heat-stable enterotoxin II signal sequence	(synthetic)		(synthetic)	Lee et al. (1983) Infect. Immunol. 264-268
M41	AflII-lacI-NheI	lac-repressor	BstXI, MluI,BbsI, BanII, BstEII, HpaI, BbeI, VspI		pASK30	see M1
M42	EcoRI-Histail-HindIII	poly-histidine tail	(synthetic)		(synthetic)	Lindner et al., (1992) Methods: a companion to methods in enzymology 4, 41-56

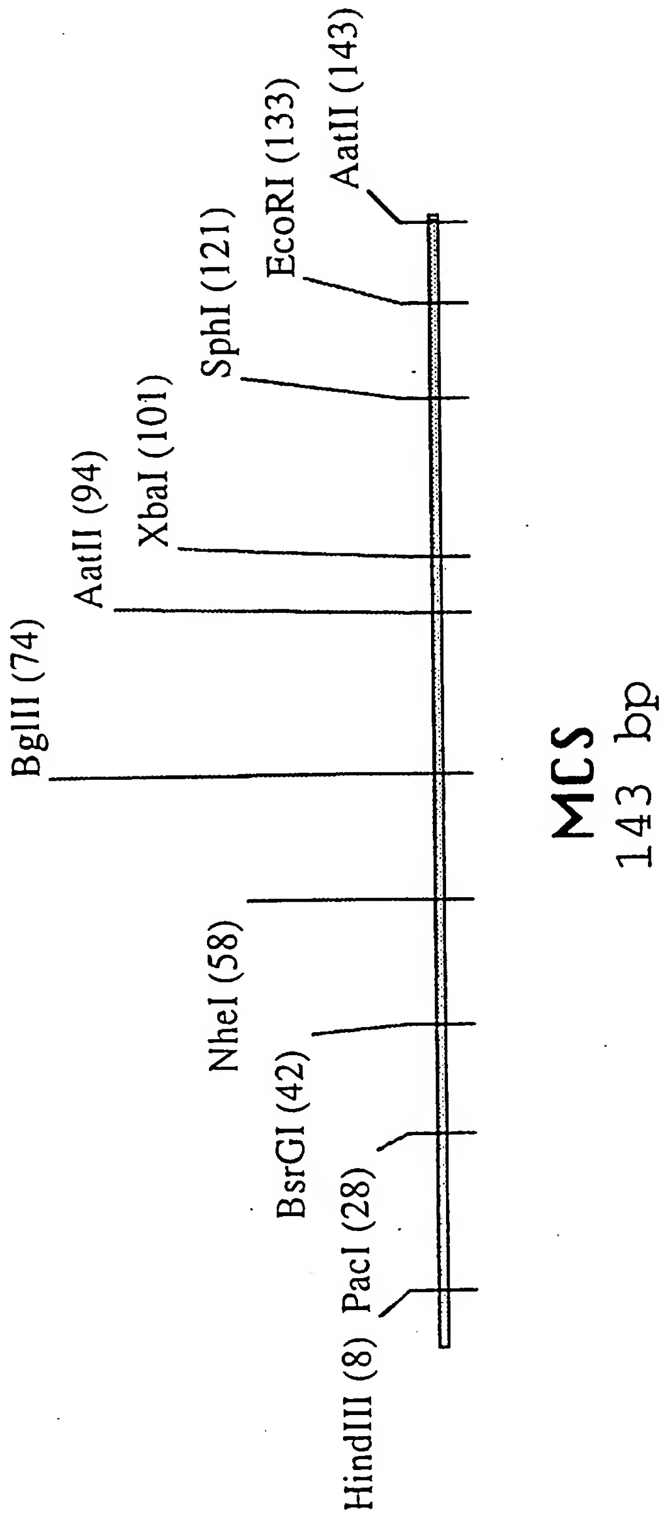


Figure 27: functional map and sequence of MCS module

Figure 27: functional map and sequence of MCS module (continued)

```
             HindIII                       PacI                        BsrGI
             ~~~~~~~~                    ~~~~~~~~~                    ~~~~~~
  1   ACATGTAAGC TTCCCCCCCC CCTTAATTAA CCCCCCCCCC TGTACACCCC
      TGTACATTCG AAGGGGGGGG GGAATTAATT GGGGGGGGGG ACATGTGGGG

              NheI                     BglII                  AatII    XbaI
             ~~~~~~~~                 ~~~~~~                ~~~~~~~~      ~
 51   CCCCCCGCTA GCCCCCCCCC CCAGATCTCC CCCCCCCCGA CGTCCCCCCT
      GGGGGGCGAT CGGGGGGGGG GGTCTAGAGG GGGGGGGGCT GCAGGGGGGA

      XbaI               SphI                      EcoRI AatII
      ~~~~~             ~~~~~~~~                  ~~~~~~~~~~~~
101   CTAGACCCCC CCCCCGCATG CCCCCCCCCC CGAATTCGAC GTC
      GATCTGGGGG GGGGGCGTAC GGGGGGGGGG GCTTAAGCTG CAG
```

Figure 28: functional map and sequence of pMCS cloning vector

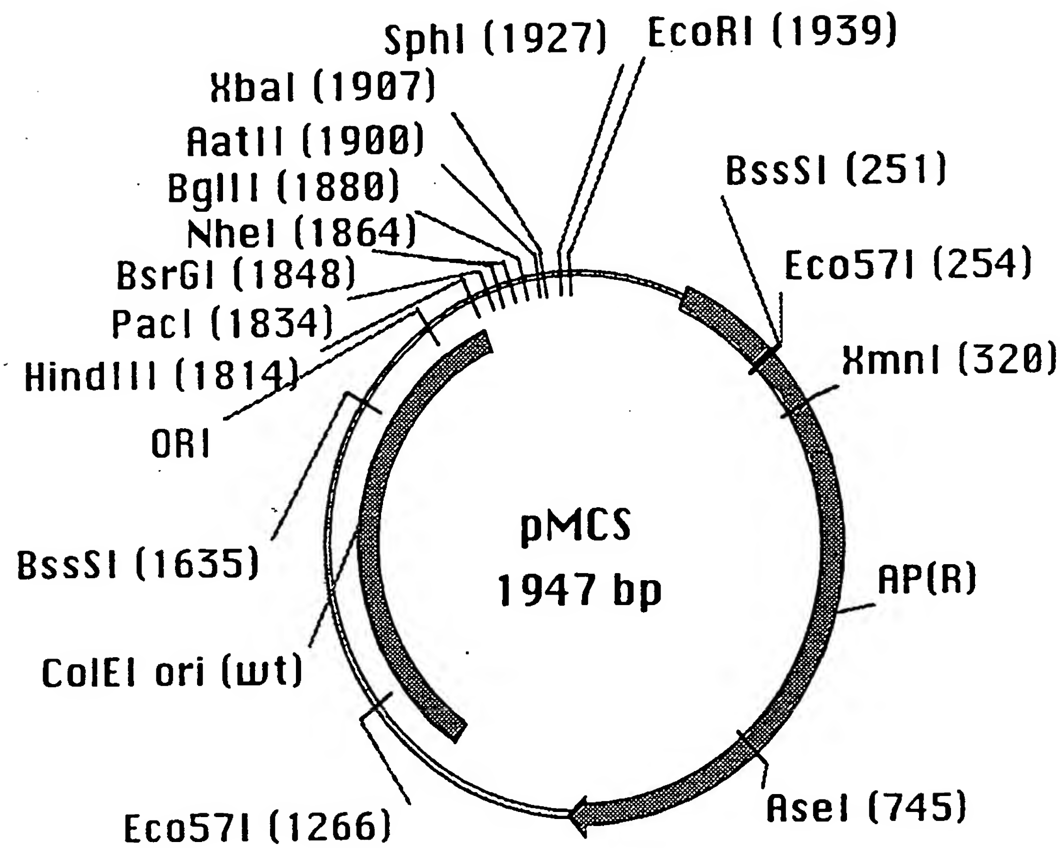


Figure 28: functional map and sequence of pMCS cloning vector (continued)

```
  1  CAGGTGGCAC TTTTCGGGGA AATGTGCGCG GAACCCCTAT TTGTTTATTT
     GTCCACCGTG AAAAGCCCCT TTACACGCGC CTTGGGGATA AACAAATAAA

 51  TTCTAAATAC ATTCAAATAT GTATCCGCTC ATGAGACAAT AACCCTGATA
     AAGATTTATG TAAGTTTATA CATAGGCGAG TACTCTGTTA TTGGGACTAT

101  AATGCTTCAA TAATATTGAA AAAGGAAGAG TATGAGTATT CAACATTTCC
     TTACGAAGTT ATTATAACTT TTTCCTTCTC ATACTCATAA GTTGTAAAGG

151  GTGTCGCCCT TATTCCCTTT TTTGCGGCAT TTTGCCTTCC TGTTTTTGCT
     CACAGCGGGA ATAAGGGAAA AAACGCCGTA AAACGGAAGG ACAAAAACGA

                                      Eco57I
                                      ~~~~~~
201  CACCCAGAAA CGCTGGTGAA AGTAAAAGAT GCTGAAGATC AGTTGGGTGC
     GTGGGTCTTT GCGACCACTT TCATTTTCTA CGACTTCTAG TCAACCCACG
                                                     BssSI
                                                         ~

251  ACGAGTGGGT TACATCGAAC TGGATCTCAA CAGCGGTAAG ATCCTTGAGA
     TGCTCACCCA ATGTAGCTTG ACCTAGAGTT GTCGCCATTC TAGGAACTCT
     BssSI
     ~~~~~
```

Figure 28: functional map and sequence of pMCS cloning vector (continued)

```
                          XmnI
                       ~~~~~~~~~~~~
301  GTTTTCGCCC CGAAGAACGT TTTCCAATGA TGAGCACTTT TAAAGTTCTG
     CAAAAGCGGG GCTTCTTGCA AAAGGTTACT ACTCGTGAAA ATTTCAAGAC

351  CTATGTGGCG CGGTATTATC CCGTATTGAC GCCGGGCAAG AGCAACTCGG
     GATACACCGC GCCATAATAG GGCATAACTG CGGCCCGTTC TCGTTGAGCC

401  TCGCCGCATA CACTATTCTC AGAATGACTT GGTTGAGTAC TCACCAGTCA
     AGCGGCGTAT GTGATAAGAG TCTTACTGAA CCAACTCATG AGTGGTCAGT

451  CAGAAAAGCA TCTTACGGAT GGCATGACAG TAAGAGAATT ATGCAGTGCT
     GTCTTTTCGT AGAATGCCTA CCGTACTGTC ATTCTCTTAA TACGTCACGA

501  GCCATAACCA TGAGTGATAA CACTGCGGCC AACTTACTTC TGACAACGAT
     CGGTATTGGT ACTCACTATT GTGACGCCGG TTGAATGAAG ACTGTTGCTA

551  CGGAGGACCG AAGGAGCTAA CCGCTTTTTT GCACAACATG GGGGATCATG
     GCCTCCTGGC TTCCTCGATT GGCGAAAAAA CGTGTTGTAC CCCCTAGTAC

601  TAACTCGCCT TGATCGTTGG GAACCGGAGC TGAATGAAGC CATACCAAAC
     ATTGAGCGGA ACTAGCAACC CTTGGCCTCG ACTTACTTCG GTATGGTTTG

651  GACGAGCGTG ACACCACGAT GCCTGTAGCA ATGGCAACAA CGTTGCGCAA
```

Figure 28: functional map and sequence of pMCS cloning vector (continued)

```
      CTGCTCGCAC TGTGGTGCTA CGGACATCGT TACCGTTGTT GCAACGCGTT

                                                   AseI
                                                  ~~~~~~~
701   ACTATTAACT GGCGAACTAC TTACTCTAGC TTCCCGGCAA CAATTAATAG
      TGATAATTGA CCGCTTGATG AATGAGATCG AAGGGCCGTT GTTAATTATC

751   ACTGGATGGA GGCGGATAAA GTTGCAGGAC CACTTCTGCG CTCGGCCCTT
      TGACCTACCT CCGCCTATTT CAACGTCCTG GTGAAGACGC GAGCCGGGAA

801   CCGGCTGGCT GGTTTATTGC TGATAAATCT GGAGCCGGTG AGCGTGGGTC
      GGCCGACCGA CCAAATAACG ACTATTTAGA CCTCGGCCAC TCGCACCCAG

851   TCGCGGTATC ATTGCAGCAC TGGGGCCAGA TGGTAAGCCC TCCCGTATCG
      AGCGCCATAG TAACGTCGTG ACCCCGGTCT ACCATTCGGG AGGGCATAGC

901   TAGTTATCTA CACGACGGGG AGTCAGGCAA CTATGGATGA ACGAAATAGA
      ATCAATAGAT GTGCTGCCCC TCAGTCCGTT GATACCTACT TGCTTTATCT

951   CAGATCGCTG AGATAGGTGC CTCACTGATT AAGCATTGGT AACTGTCAGA
      GTCTAGCGAC TCTATCCACG GAGTGACTAA TTCGTAACCA TTGACAGTCT

1001  CCAAGTTTAC TCATATATAC TTTAGATTGA TTTAAAACTT CATTTTTAAT
      GGTTCAAATG AGTATATATG AAATCTAACT AAATTTTGAA GTAAAAATTA
```

Figure 28: functional map and sequence of pMCS cloning vector (continued)

```
1051  TTAAAAGGAT CTAGGTGAAG ATCCTTTTTG ATAATCTCAT GACCAAAATC
      AATTTTCCTA GATCCACTTC TAGGAAAAAC TATTAGAGTA CTGGTTTTAG

1101  CCTTAACGTG AGTTTTCGTT CCACTGAGCG TCAGACCCCG TAGAAAAGAT
      GGAATTGCAC TCAAAAGCAA GGTGACTCGC AGTCTGGGGC ATCTTTTCTA

1151  CAAAGGATCT TCTTGAGATC CTTTTTTTCT GCGCGTAATC TGCTGCTTGC
      GTTTCCTAGA AGAACTCTAG GAAAAAAAGA CGCGCATTAG ACGACGAACG

1201  AAACAAAAAA ACCACCGCTA CCAGCGGTGG TTTGTTTGCC GGATCAAGAG
      TTTGTTTTTT TGGTGGCGAT GGTCGCCACC AAACAAACGG CCTAGTTCTC

1251  CTACCAACTC TTTTTCCGAA GGTAACTGGC TTCAGCAGAG CGCAGATACC
      GATGGTTGAG AAAAAGGCTT CCATTGACCG AAGTCGTCTC GCGTCTATGG
                                         Eco57I
          -                              ~~~~~~~~

1301  AAATACTGTC CTTCTAGTGT AGCCGTAGTT AGGCCACCAC TTCAAGAACT
      TTTATGACAG GAAGATCACA TCGGCATCAA TCCGGTGGTG AAGTTCTTGA

1351  CTGTAGCACC GCCTACATAC CTCGCTCTGC TAATCCTGTT ACCAGTGGCT
      GACATCGTGG CGGATGTATG GAGCGAGACG ATTAGGACAA TGGTCACCGA
```

Figure 28: functional map and sequence of pMCS cloning vector (continued)

```
1401   GCTGCCAGTG GCGATAAGTC GTGTCTTACC GGGTTGGACT CAAGACGATA
       CGACGGTCAC CGCTATTCAG CACAGAATGG CCCAACCTGA GTTCTGCTAT

1451   GTTACCGGAT AAGGCGCAGC GGTCGGGCTG AACGGGGGGT TCGTGCACAC
       CAATGGCCTA TTCCGCGTCG CCAGCCCGAC TTGCCCCCCA AGCACGTGTG

1501   AGCCCAGCTT GGAGCGAACG ACCTACACCG AACTGAGATA CCTACAGCGT
       TCGGGTCGAA CCTCGCTTGC TGGATGTGGC TTGACTCTAT GGATGTCGCA

1551   GAGCTATGAG AAAGCGCCAC GCTTCCCGAA GGGAGAAAGG CGGACAGGTA
       CTCGATACTC TTTCGCGGTG CGAAGGGCTT CCCTCTTTCC GCCTGTCCAT

1601   TCCGGTAAGC GGCAGGGTCG GAACAGGAGA GCGCACGAGG GAGCTTCCAG
       AGGCCATTCG CCGTCCCAGC CTTGTCCTCT CGCGTGCTCC CTCGAAGGTC
                                             BssSI
                                            ~~~~~~

1651   GGGGAAACGC CTGGTATCTT TATAGTCCTG TCGGGTTTCG CCACCTCTGA
       CCCCTTTGCG GACCATAGAA ATATCAGGAC AGCCCAAAGC GGTGGAGACT

1701   CTTGAGCGTC GATTTTTGTG ATGCTCGTCA GGGGGGCGGA GCCTATGGAA
       GAACTCGCAG CTAAAAACAC TACGAGCAGT CCCCCCGCCT CGGATACCTT

1751   AAACGCCAGC AACGCGGCCT TTTTACGGTT CCTGGCCTTT TGCTGGCCTT
```

Figure 28: functional map and sequence of pMCS cloning vector (continued)

```
          TTTGCGGTCG TTGCGCCGGA AAAATGCCAA GGACCGGAAA ACGACCGGAA

                      HindIII               PacI           BsrGI
                      ~~~~~~~           ~~~~~~~~~~          ~~~~
1801      TTGCTCACAT GTAAGCTTCC CCCCCCCCTT AATTAACCCC CCCCCCTGTA
          AACGAGTGTA CATTCGAAGG GGGGGGGGAA TTAATTGGGG GGGGGGACAT

          BsrGI        NheI                BglII           AatII
          ~~          ~~~~~~~          ~~~~~~~~          ~~~~~~~
1851      CACCCCCCCC CCGCTAGCCC CCCCCCCCAG ATCTCCCCCC CCCCGACGTC
          GTGGGGGGGG GGCGATCGGG GGGGGGGGTC TAGAGGGGGG GGGGCTGCAG

               XbaI                SphI             EcoRI
             ~~~~~~~~            ~~~~~~~          ~~~~~~~~
1901      CCCCCTCTAG ACCCCCCCCC CGCATGCCCC CCCCCCCGAA TTCACGT
          GGGGGAGATC TGGGGGGGGG GCGTACGGGG GGGGGGGCTT AAGTGCA
```

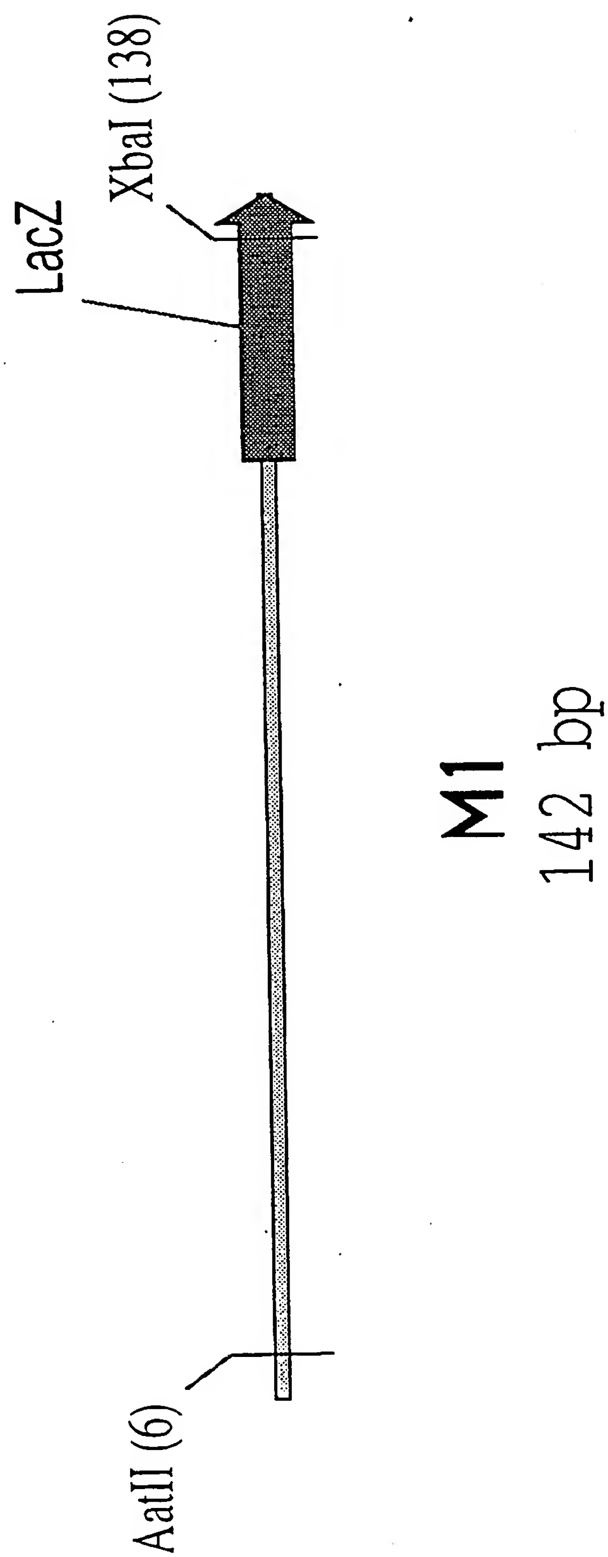


Figure 29: functional map and sequence of pCAL module M1

Figure 29: functional map and sequence of pCAL module M1

```
         AatII
         ~~~~~~~
  1      GACGTCTTAA TGTGAGTTAG CTCACTCATT AGGCACCCCA GGCTTTACAC
         CTGCAGAATT ACACTCAATC GAGTGAGTAA TCCGTGGGGT CCGAAATGTG

 51      TTTATGCTTC CGGCTCGTAT GTTGTGTGGA ATTGTGAGCG GATAACAATT
         AAATACGAAG GCCGAGCATA CAACACACCT TAACACTCGC CTATTGTTAA

                                                 XbaI
                                               ~~~~~~~
101      TCACACAGGA AACAGCTATG ACCATGATTA CGAATTTCTA GA
         AGTGTGTCCT TTGTCGATAC TGGTACTAAT GCTTAAAGAT CT
```

Figure 30: functional map and sequence of pCAL module M7-II

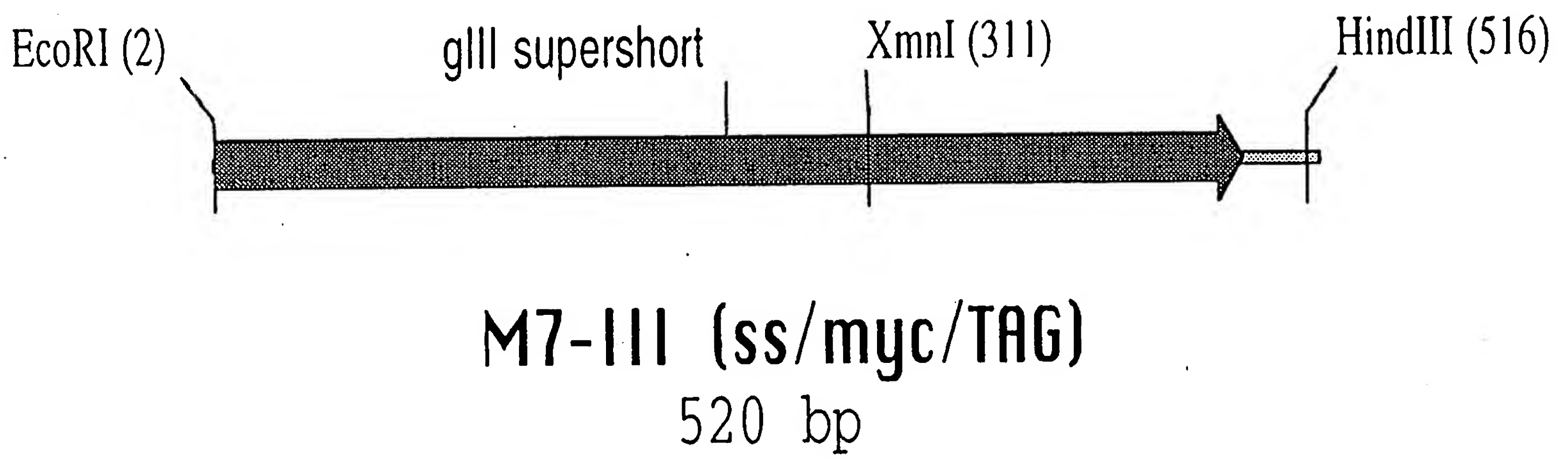


Figure 30: functional map and sequence of pCAL module M7-II (continued)

```
        EcoRI
       ~~~~~~~
  1    GAATTCGAGC AGAAGCTGAT CTCTGAGGAG GATCTGTAGG GTGGTGGCTC
       CTTAAGCTCG TCTTCGACTA GAGACTCCTC CTAGACATCC CACCACCGAG

 51    TGGTTCCGGT GATTTTGATT ATGAAAAGAT GGCAAACGCT AATAAGGGGG
       ACCAAGGCCA CTAAAACTAA TACTTTTCTA CCGTTTGCGA TTATTCCCCC

101    CTATGACCGA AAATGCCGAT GAAAACGCGC TACAGTCTGA CGCTAAAGGC
       GATACTGGCT TTTACGGCTA CTTTTGCGCG ATGTCAGACT GCGATTTCCG

151    AAACTTGATT CTGTCGCTAC TGATTACGGT GCTGCTATCG ATGGTTTCAT
       TTTGAACTAA GACAGCGATG ACTAATGCCA CGACGATAGC TACCAAAGTA

201    TGGTGACGTT TCCGGCCTTG CTAATGGTAA TGGTGCTACT GGTGATTTTG
       ACCACTGCAA AGGCCGGAAC GATTACCATT ACCACGATGA CCACTAAAAC

251    CTGGCTCTAA TTCCCAAATG GCTCAAGTCG GTGACGGTGA TAATTCACCT
       GACCGAGATT AAGGGTTTAC CGAGTTCAGC CACTGCCACT ATTAAGTGGA

                  XmnI
              ~~~~~~~~~~~~
301    TTAATGAATA ATTTCCGTCA ATATTTACCT TCCCTCCCTC AATCGGTTGA
       AATTACTTAT TAAAGGCAGT TATAAATGGA AGGGAGGGAG TTAGCCAACT
```

Figure 30: functional map and sequence of pCAL module M7-II (continued)

```
351   ATGTCGCCCT TTTGTCTTTG GCGCTGGTAA ACCATATGAA TTTTCTATTG
      TACAGCGGGA AAACAGAAAC CGCGACCATT TGGTATACTT AAAAGATAAC

401   ATTGTGACAA AATAAACTTA TTCCGTGGTG TCTTTGCGTT TCTTTTATAT
      TAACACTGTT TTATTTGAAT AAGGCACCAC AGAAACGCAA AGAAAATATA

451   GTTGCCACCT TTATGTATGT ATTTTCTACG TTTGCTAACA TACTGCGTAA
      CAACGGTGGA AATACATACA TAAAAGATGC AAACGATTGT ATGACGCATT

                     HindIII
                     ~~~~~~
501   TAAGGAGTCT TGATAAGCTT
      ATTCCTCAGA ACTATTCGAA
```

Figure 31: functional map and sequence of pCAL module M9-II

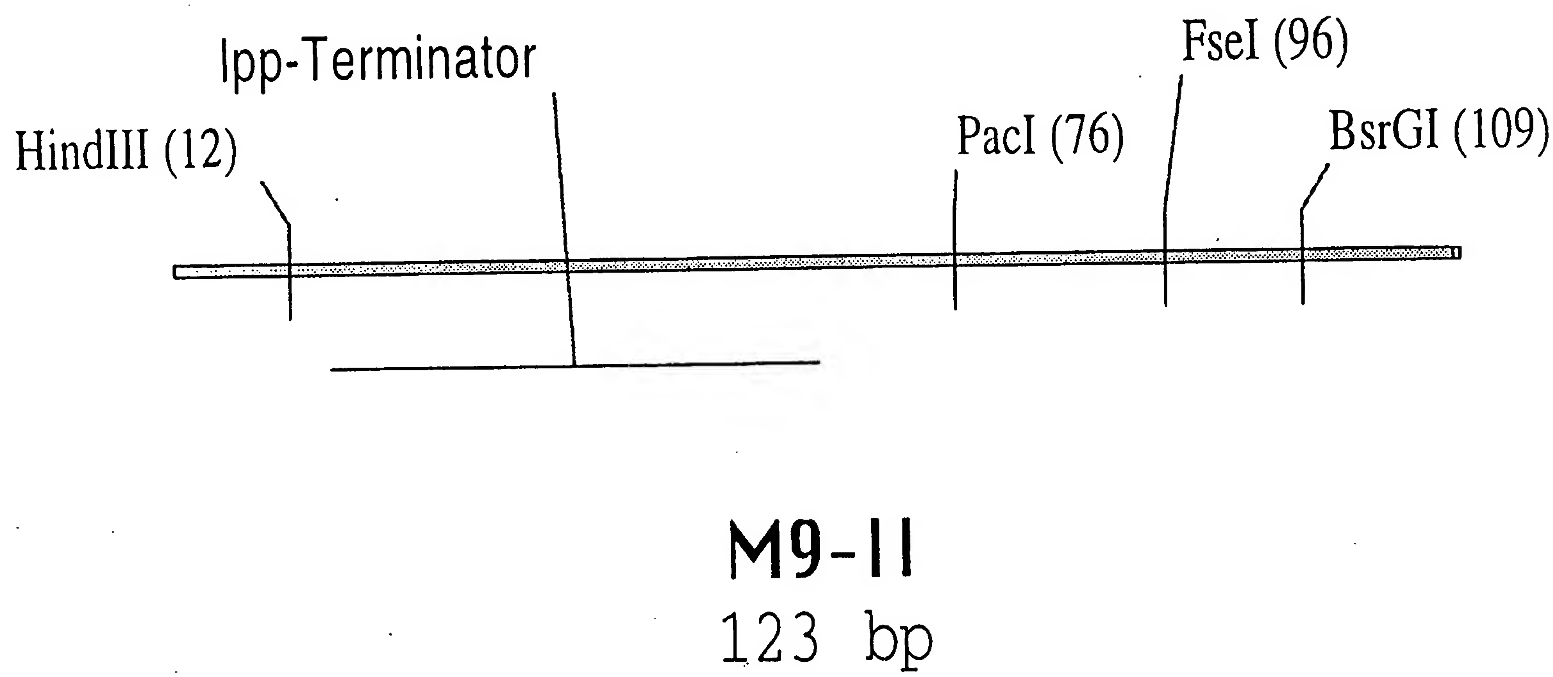


Figure 31: functional map and sequence of pCAL module M9-II (continued)

```
                HindIII
                ~~~~~~~
  1  GGGGGGGGGG AAGCTTGACC TGTGAAGTGA AAAATGGCGC AGATTGTGCG
     CCCCCCCCCC TTCGAACTGG ACACTTCACT TTTTACCGCG TCTAACACGC

                            PacI                   FseI
                          ~~~~~~~~~            ~~~~~~~~~~
 51  ACATTTTTTT TGTCTGCCGT TTAATTAAAG GGGGGGGGGG GCCGGCCTGG
     TGTAAAAAAA ACAGACGGCA AATTAATTTC CCCCCCCCCC CGGCCGGACC

            BsrGI
          ~~~~~~~~
101  GGGGGGGTGT ACAGGGGGGG GGG
     CCCCCCCACA TGTCCCCCCC CCC
```

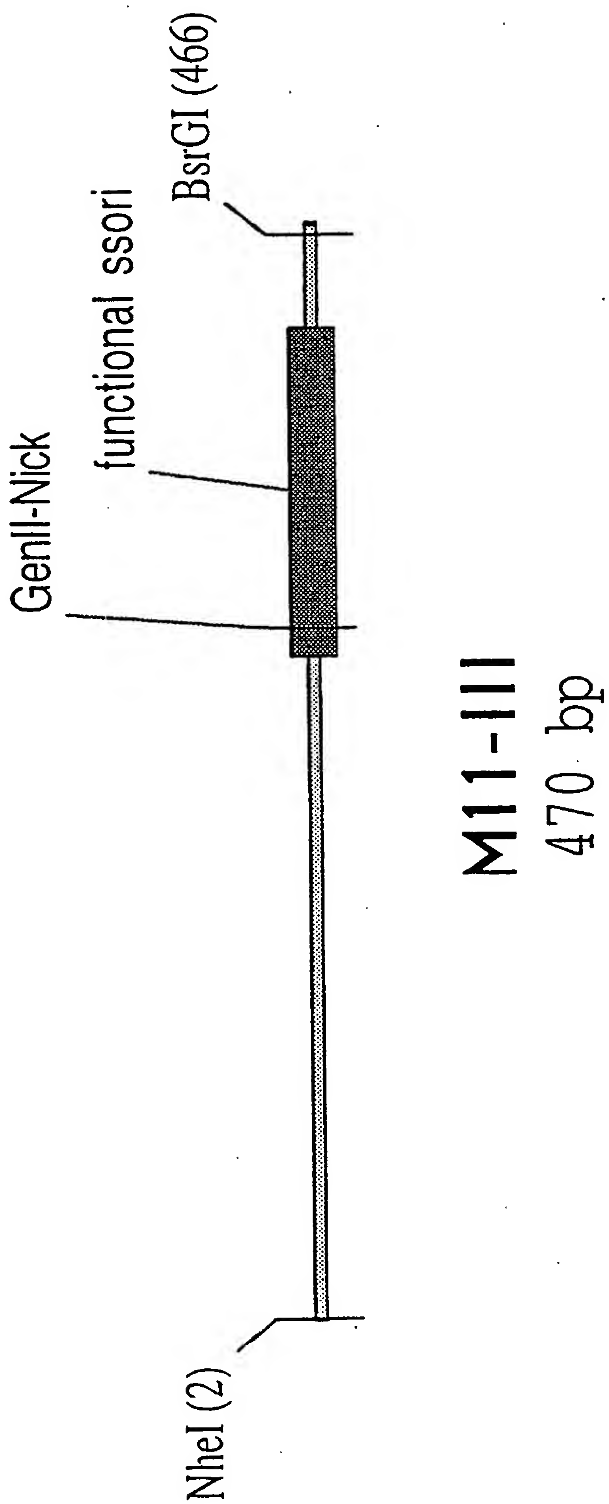


Figure 32: functional map and sequence of pCAL module M11-III

Figure 32: functional map and sequence of pCAL module M11-III (continued)

```
          NheI
          ~~~~~~
  1   GCTAGCACGC GCCCTGTAGC GGCGCATTAA GCGCGGCGGG TGTGGTGGTT
      CGATCGTGCG CGGGACATCG CCGCGTAATT CGCGCCGCCC ACACCACCAA

 51   ACGCGCAGCG TGACCGCTAC ACTTGCCAGC GCCCTAGCGC CCGCTCCTTT
      TGCGCGTCGC ACTGGCGATG TGAACGGTCG CGGGATCGCG GGCGAGGAAA

101   CGCTTTCTTC CCTTCCTTTC TCGCCACGTT CGCCGGCTTT CCCCGTCAAG
      GCGAAAGAAG GGAAGGAAAG AGCGGTGCAA GCGGCCGAAA GGGGCAGTTC

151   CTCTAAATCG GGGCATCCCT TTAGGGTTCC GATTTAGTGC TTTACGGCAC
      GAGATTTAGC CCCGTAGGGA AATCCCAAGG CTAAATCACG AAATGCCGTG

201   CTCGACCCCA AAAAACTTGA TTAGGGTGAT GGTTCTCGTA GTGGGCCATC
      GAGCTGGGGT TTTTTGAACT AATCCCACTA CCAAGAGCAT CACCCGGTAG

251   GCCCTGATAG ACGGTTTTTC GCCCTTTGAC GTTGGAGTCC ACGTTCTTTA
      CGGGACTATC TGCCAAAAAG CGGGAAACTG CAACCTCAGG TGCAAGAAAT

301   ATAGTGGACT CTTGTTCCAA ACTGGAACAA CACTCAACCC TATCTCGGTC
      TATCACCTGA GAACAAGGTT TGACCTTGTT GTGAGTTGGG ATAGAGCCAG

351   TATTCTTTTG ATTTATAAGG GATTTTGCCG ATTTCGGCCT ATTGGTTAAA
```

Figure 32: functional map and sequence of pCAL module M11-III (continued)

```
       ATAAGAAAAC TAAATATTCC CTAAAACGGC TAAAGCCGGA TAACCAATTT

401    AAATGAGCTG ATTTAACAAA AATTTAACGC GAATTTTAAC AAAATATTAA
       TTTACTCGAC TAAATTGTTT TTAAATTGCG CTTAAAATTG TTTTATAATT

                        BsrGI
                       ~~~~~~~
451    CGTTTACAAT TTCATGTACA
       GCAAATGTTA AAGTACATGT
```

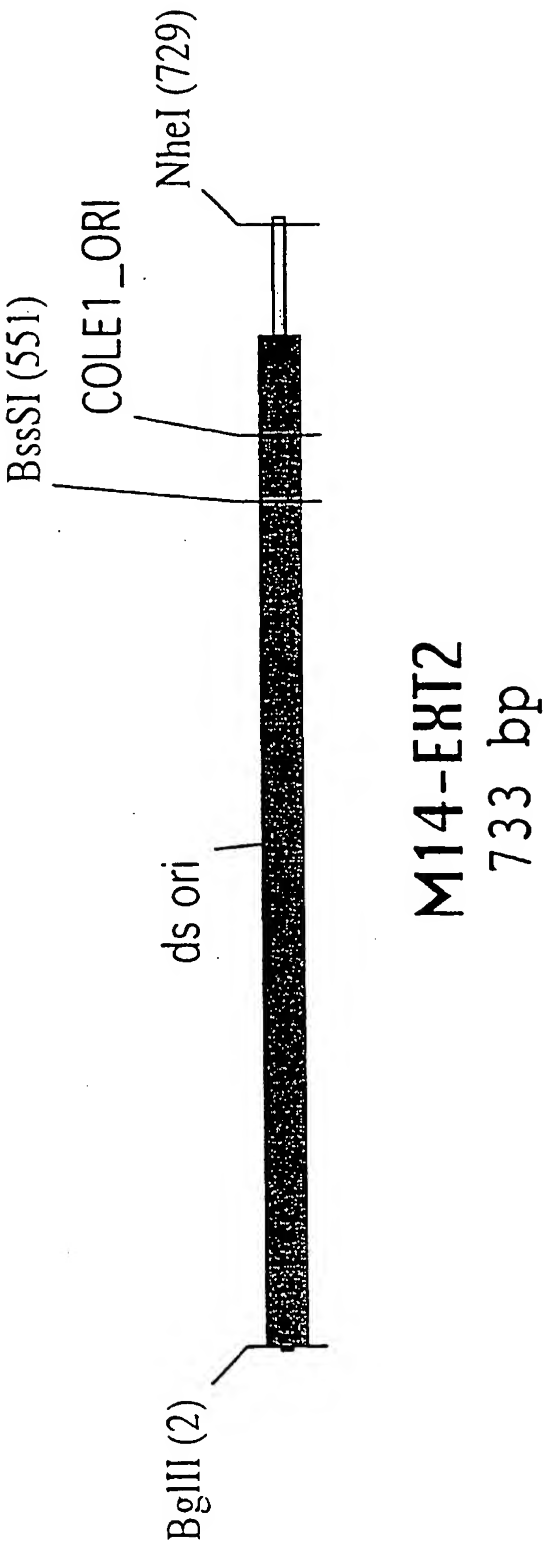


Figure 33: functional map and sequence of pCAL module M14-Ext2

Figure 33: functional map and sequence of pCAL module M14-Ext2 (continued)

```
          BglII
          ~~~~~~~
  1       AGATCTGACC AAAATCCCTT AACGTGAGTT TTCGTTCCAC TGAGCGTCAG
          TCTAGACTGG TTTTAGGGAA TTGCACTCAA AAGCAAGGTG ACTCGCAGTC

 51       ACCCCGTAGA AAAGATCAAA GGATCTTCTT GAGATCCTTT TTTTCTGCGC
          TGGGGCATCT TTTCTAGTTT CCTAGAAGAA CTCTAGGAAA AAAAGACGCG

101       GTAATCTGCT GCTTGCAAAC AAAAAAACCA CCGCTACCAG CGGTGGTTTG
          CATTAGACGA CGAACGTTTG TTTTTTTGGT GGCGATGGTC GCCACCAAAC

151       TTTGCCGGAT CAAGAGCTAC CAACTCTTTT TCCGAAGGTA ACTGGCTACA
          AAACGGCCTA GTTCTCGATG GTTGAGAAAA AGGCTTCCAT TGACCGATGT

201       GCAGAGCGCA GATACCAAAT ACTGTTCTTC TAGTGTAGCC GTAGTTAGGC
          CGTCTCGCGT CTATGGTTTA TGACAAGAAG ATCACATCGG CATCAATCCG

251       CACCACTTCA AGAACTCTGT AGCACCGCCT ACATACCTCG CTCTGCTAAT
          GTGGTGAAGT TCTTGAGACA TCGTGGCGGA TGTATGGAGC GAGACGATTA

301       CCTGTTACCA GTGGCTGCTG CCAGTGGCGA TAAGTCGTGT CTTACCGGGT
          GGACAATGGT CACCGACGAC GGTCACCGCT ATTCAGCACA GAATGGCCCA

351       TGGACTCAAG ACGATAGTTA CCGGATAAGG CGCAGCGGTC GGGCTGAACG
```

Figure 33: functional map and sequence of pCAL module M14-Ext2 (continued)

```
     ACCTGAGTTC TGCTATCAAT GGCCTATTCC GCGTCGCCAG CCCGACTTGC

401  GGGGGTTCGT GCACACAGCC CAGCTTGGAG CGAACGACCT ACACCGAACT
     CCCCCAAGCA CGTGTGTCGG GTCGAACCTC GCTTGCTGGA TGTGGCTTGA

451  GAGATACCTA CAGCGTGAGC TATGAGAAAG CGCCACGCTT CCCGAAGGGA
     CTCTATGGAT GTCGCACTCG ATACTCTTTC GCGGTGCGAA GGGCTTCCCT

501  GAAAGGCGGA CAGGTATCCG GTAAGCGGCA GGGTCGGAAC AGGAGAGCGC
     CTTTCCGCCT GTCCATAGGC CATTCGCCGT CCCAGCCTTG TCCTCTCGCG
                                                      BssSI
                                                          ~

551  ACGAGGGAGC TTCCAGGGGG AAACGCCTGG TATCTTTATA GTCCTGTCGG
     TGCTCCCTCG AAGGTCCCCC TTTGCGGACC ATAGAAATAT CAGGACAGCC
     BssSI
     ~~~~~

601  GTTTCGCCAC CTCTGACTTG AGCGTCGATT TTTGTGATGC TCGTCAGGGG
     CAAAGCGGTG GAGACTGAAC TCGCAGCTAA AAACACTACG AGCAGTCCCC

651  GGCGGAGCCT ATGGAAAAAC GCCAGCAACG CGGCCTTTTT ACGGTTCCTG
     CCGCCTCGGA TACCTTTTTG CGGTCGTTGC GCCGGAAAAA TGCCAAGGAC
```

Figure 33: functional map and sequence of pCAL module M14-Ext2 (continued)

```
                                            NheI
                                          ~~~~~~
701  GCCTTTTGCT GGCCTTTTGC TCACATGGCT AGC
     CGGAAAACGA CCGGAAAACG AGTGTACCGA TCG
```

Figure 34: functional map and sequence of pCAL module M17

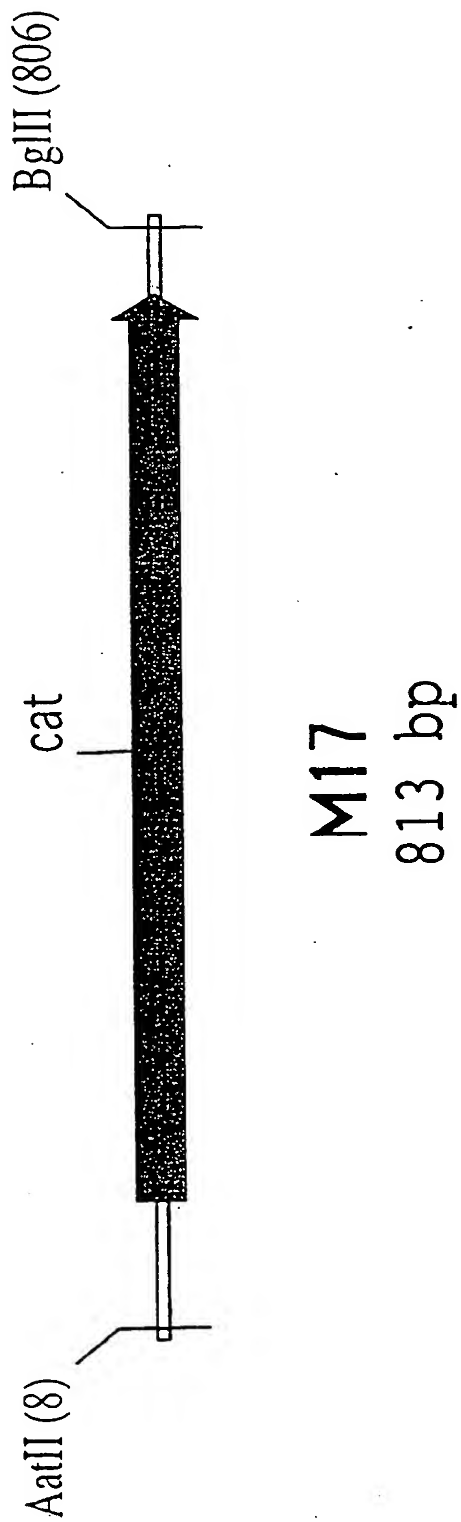


Figure 34: functional map and sequence of pCAL module M17 (continued)

```
         AatII
        ~~~~~~~
  1   GGGACGTCGG GTGAGGTTCC AACTTTCACC ATAATGAAAT AAGATCACTA
      CCCTGCAGCC CACTCCAAGG TTGAAAGTGG TATTACTTTA TTCTAGTGAT

 51   CCGGGCGTAT TTTTTGAGTT ATCGAGATTT TCAGGAGCTA AGGAAGCTAA
      GGCCCGCATA AAAAACTCAA TAGCTCTAAA AGTCCTCGAT TCCTTCGATT

101   AATGGAGAAA AAAATCACTG GATATACCAC CGTTGATATA TCCCAATGGC
      TTACCTCTTT TTTTAGTGAC CTATATGGTG GCAACTATAT AGGGTTACCG

151   ATCGTAAAGA ACATTTTGAG GCATTTCAGT CAGTTGCTCA ATGTACCTAT
      TAGCATTTCT TGTAAAACTC CGTAAAGTCA GTCAACGAGT TACATGGATA

201   AACCAGACCG TTCAGCTGGA TATTACGGCC TTTTTAAAGA CCGTAAAGAA
      TTGGTCTGGC AAGTCGACCT ATAATGCCGG AAAAATTTCT GGCATTTCTT

251   AAATAAGCAC AAGTTTTATC CGGCCTTTAT TCACATTCTT GCCCGCCTGA
      TTTATTCGTG TTCAAAATAG GCCGGAAATA AGTGTAAGAA CGGGCGGACT

301   TGAATGCTCA CCCGGAGTTC CGTATGGCAA TGAAAGACGG TGAGCTGGTG
      ACTTACGAGT GGGCCTCAAG GCATACCGTT ACTTTCTGCC ACTCGACCAC

351   ATATGGGATA GTGTTCACCC TTGTTACACC GTTTTCCATG AGCAAACTGA
```

Figure 34: functional map and sequence of pCAL module M17 (continued)

```
     TATACCCTAT CACAAGTGGG AACAATGTGG CAAAAGGTAC TCGTTTGACT

401  AACGTTTTCA TCGCTCTGGA GTGAATACCA CGACGATTTC CGGCAGTTTC
     TTGCAAAAGT AGCGAGACCT CACTTATGGT GCTGCTAAAG GCCGTCAAAG

451  TACACATATA TTCGCAAGAT GTGGCGTGTT ACGGTGAAAA CCTGGCCTAT
     ATGTGTATAT AAGCGTTCTA CACCGCACAA TGCCACTTTT GGACCGGATA

501  TTCCCTAAAG GGTTTATTGA GAATATGTTT TTCGTCTCAG CCAATCCCTG
     AAGGGATTTC CCAAATAACT CTTATACAAA AAGCAGAGTC GGTTAGGGAC

551  GGTGAGTTTC ACCAGTTTTG ATTTAAACGT AGCCAATATG GACAACTTCT
     CCACTCAAAG TGGTCAAAAC TAAATTTGCA TCGGTTATAC CTGTTGAAGA

601  TCGCCCCCGT TTTCACTATG GGCAAATATT ATACGCAAGG CGACAAGGTG
     AGCGGGGGCA AAAGTGATAC CCGTTTATAA TATGCGTTCC GCTGTTCCAC

651  CTGATGCCGC TGGCGATTCA GGTTCATCAT GCCGTTTGTG ATGGCTTCCA
     GACTACGGCG ACCGCTAAGT CCAAGTAGTA CGGCAAACAC TACCGAAGGT

701  TGTCGGCAGA ATGCTTAATG AATTACAACA GTACTGCGAT GAGTGGCAGG
     ACAGCCGTCT TACGAATTAC TTAATGTTGT CATGACGCTA CTCACCGTCC

751  GCGGGGCGTA ATTTTTTTAA GGCAGTTATT GGGTGCCCTT AAACGCCTGG
```

Figure 34: functional map and sequence of pCAL module M17 (continued)

```
     CGCCCCGCAT TAAAAAAATT CCGTCAATAA CCCACGGGAA TTTGCGGACC

         BglII
        ~~~~~~
801  TGCTAGATCT TCC
     ACGATCTAGA AGG
```

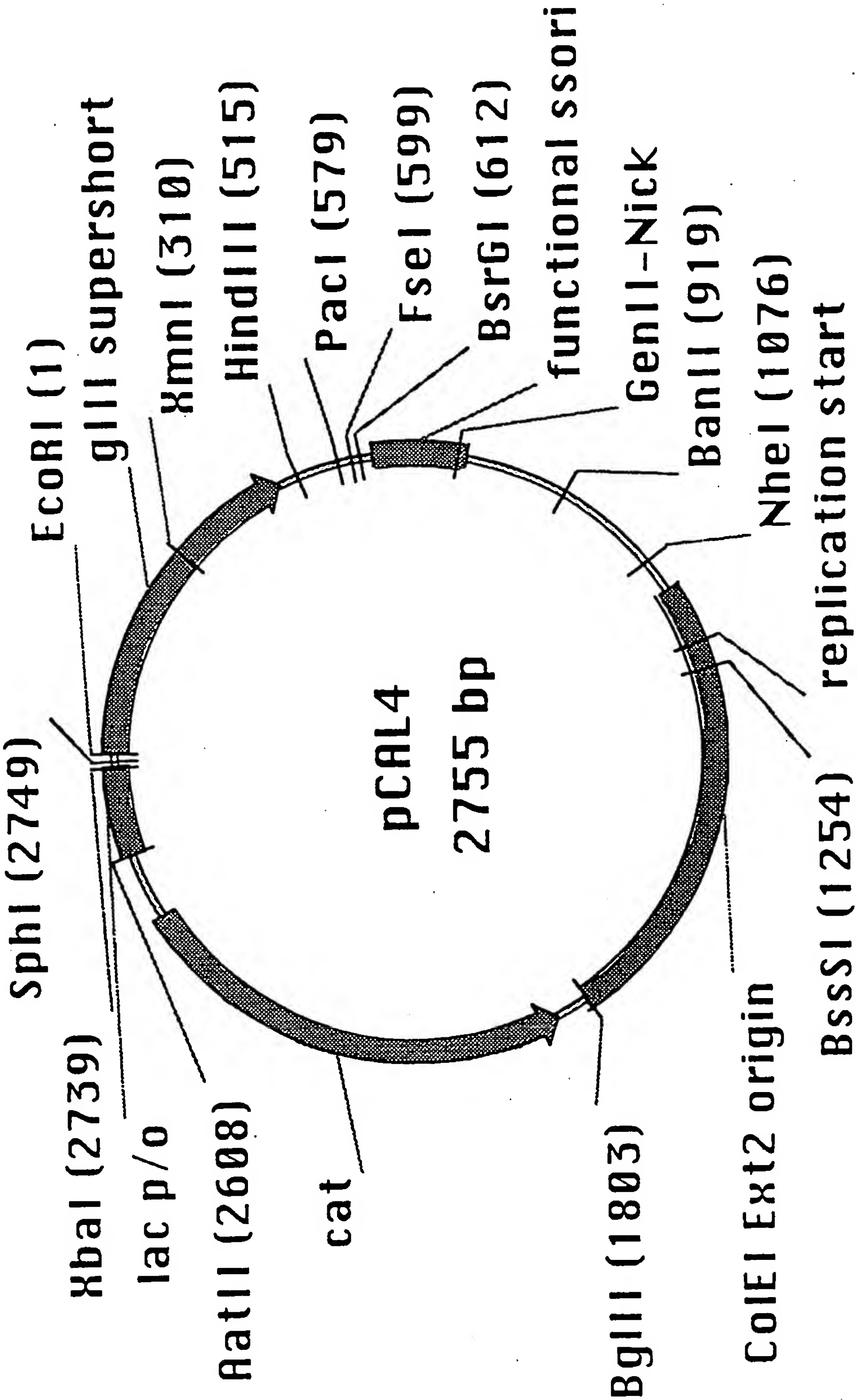


Figure 35: functional map and sequence of modular vector pCAL4

Figure 35: functional map and sequence of modular vector pCAL4 (continued)

```
        EcoRI
        ~~~~~~
  1     AATTCGAGCA GAAGCTGATC TCTGAGGAGG ATCTGTAGGG TGGTGGCTCT
        TTAAGCTCGT CTTCGACTAG AGACTCCTCC TAGACATCCC ACCACCGAGA

 51     GGTTCCGGTG ATTTTGATTA TGAAAAGATG GCAAACGCTA ATAAGGGGGC
        CCAAGGCCAC TAAAACTAAT ACTTTTCTAC CGTTTGCGAT TATTCCCCCG

101     TATGACCGAA AATGCCGATG AAAACGCGCT ACAGTCTGAC GCTAAAGGCA
        ATACTGGCTT TTACGGCTAC TTTTGCGCGA TGTCAGACTG CGATTTCCGT

151     AACTTGATTC TGTCGCTACT GATTACGGTG CTGCTATCGA TGGTTTCATT
        TTGAACTAAG ACAGCGATGA CTAATGCCAC GACGATAGCT ACCAAAGTAA

201     GGTGACGTTT CCGGCCTTGC TAATGGTAAT GGTGCTACTG GTGATTTTGC
        CCACTGCAAA GGCCGGAACG ATTACCATTA CCACGATGAC CACTAAAACG

251     TGGCTCTAAT TCCCAAATGG CTCAAGTCGG TGACGGTGAT AATTCACCTT
        ACCGAGATTA AGGGTTTACC GAGTTCAGCC ACTGCCACTA TTAAGTGGAA

                XmnI
            ~~~~~~~~~~~~~
301     TAATGAATAA TTTCCGTCAA TATTTACCTT CCCTCCCTCA ATCGGTTGAA
        ATTACTTATT AAAGGCAGTT ATAAATGGAA GGGAGGGAGT TAGCCAACTT
```

Figure 35: functional map and sequence of modular vector pCAL4 (continued)

```
351   TGTCGCCCTT TTGTCTTTGG CGCTGGTAAA CCATATGAAT TTTCTATTGA
      ACAGCGGGAA AACAGAAACC GCGACCATTT GGTATACTTA AAAGATAACT

401   TTGTGACAAA ATAAACTTAT TCCGTGGTGT CTTTGCGTTT CTTTTATATG
      AACACTGTTT TATTTGAATA AGGCACCACA GAAACGCAAA GAAAATATAC

451   TTGCCACCTT TATGTATGTA TTTTCTACGT TTGCTAACAT ACTGCGTAAT
      AACGGTGGAA ATACATACAT AAAAGATGCA AACGATTGTA TGACGCATTA

                 HindIII
                 ~~~~~~~
501   AAGGAGTCTT GATAAGCTTG ACCTGTGAAG TGAAAAATGG CGCAGATTGT
      TTCCTCAGAA CTATTCGAAC TGGACACTTC ACTTTTTACC GCGTCTAACA

                               PacI                FseI
                            ~~~~~~~~~~          ~~~~~~~~~
551   GCGACATTTT TTTTGTCTGC CGTTTAATTA AAGGGGGGGG GGGGCCGGCC
      CGCTGTAAAA AAAACAGACG GCAAATTAAT TTCCCCCCCC CCCCGGCCGG

              BsrGI
             ~~~~~~~
601   TGGGGGGGGG TGTACATGAA ATTGTAAACG TTAATATTTT GTTAAAATTC
      ACCCCCCCCC ACATGTACTT TAACATTTGC AATTATAAAA CAATTTTAAG
```

Figure 35: functional map and sequence of modular vector pCAL4 (continued)

```
651  GCGTTAAATT TTTGTTAAAT CAGCTCATTT TTTAACCAAT AGGCCGAAAT
     CGCAATTTAA AAACAATTTA GTCGAGTAAA AAATTGGTTA TCCGGCTTTA

701  CGGCAAAATC CCTTATAAAT CAAAAGAATA GACCGAGATA GGGTTGAGTG
     GCCGTTTTAG GGAATATTTA GTTTTCTTAT CTGGCTCTAT CCCAACTCAC

751  TTGTTCCAGT TTGGAACAAG AGTCCACTAT TAAAGAACGT GGACTCCAAC
     AACAAGGTCA AACCTTGTTC TCAGGTGATA ATTTCTTGCA CCTGAGGTTG

801  GTCAAAGGGC GAAAAACCGT CTATCAGGGC GATGGCCCAC TACGAGAACC
     CAGTTTCCCG CTTTTTGGCA GATAGTCCCG CTACCGGGTG ATGCTCTTGG

851  ATCACCCTAA TCAAGTTTTT TGGGGTCGAG GTGCCGTAAA GCACTAAATC
     TAGTGGGATT AGTTCAAAAA ACCCCAGCTC CACGGCATTT CGTGATTTAG

                       BanII
                      ~~~~~~
901  GGAACCCTAA AGGGAGCCCC CGATTTAGAG CTTGACGGGG AAAGCCGGCG
     CCTTGGGATT TCCCTCGGGG GCTAAATCTC GAACTGCCCC TTTCGGCCGC

951  AACGTGGCGA GAAAGGAAGG GAAGAAAGCG AAAGGAGCGG GCGCTAGGGC
     TTGCACCGCT CTTTCCTTCC CTTCTTTCGC TTTCCTCGCC CGCGATCCCG
```

Figure 35: functional map and sequence of modular vector pCAL4 (continued)

```
1001   GCTGGCAAGT GTAGCGGTCA CGCTGCGCGT AACCACCACA CCCGCCGCGC
       CGACCGTTCA CATCGCCAGT GCGACGCGCA TTGGTGGTGT GGGCGGCGCG

                                NheI
                               ~~~~~~
1051   TTAATGCGCC GCTACAGGGC GCGTGCTAGC CATGTGAGCA AAAGGCCAGC
       AATTACGCGG CGATGTCCCG CGCACGATCG GTACACTCGT TTTCCGGTCG

1101   AAAAGGCCAG GAACCGTAAA AAGGCCGCGT TGCTGGCGTT TTTCCATAGG
       TTTTCCGGTC CTTGGCATTT TTCCGGCGCA ACGACCGCAA AAAGGTATCC

1151   CTCCGCCCCC CTGACGAGCA TCACAAAAAT CGACGCTCAA GTCAGAGGTG
       GAGGCGGGGG GACTGCTCGT AGTGTTTTTA GCTGCGAGTT CAGTCTCCAC

1201   GCGAAACCCG ACAGGACTAT AAAGATACCA GGCGTTTCCC CCTGGAAGCT
       CGCTTTGGGC TGTCCTGATA TTTCTATGGT CCGCAAAGGG GGACCTTCGA

         BssSI
        ~~~~~~
1251   CCCTCGTGCG CTCTCCTGTT CCGACCCTGC CGCTTACCGG ATACCTGTCC
       GGGAGCACGC GAGAGGACAA GGCTGGGACG GCGAATGGCC TATGGACAGG

1301   GCCTTTCTCC CTTCGGGAAG CGTGGCGCTT TCTCATAGCT CACGCTGTAG
       CGGAAAGAGG GAAGCCCTTC GCACCGCGAA AGAGTATCGA GTGCGACATC
```

Figure 35: functional map and sequence of modular vector pCAL4 (continued)

```
1351  GTATCTCAGT TCGGTGTAGG TCGTTCGCTC CAAGCTGGGC TGTGTGCACG
      CATAGAGTCA AGCCACATCC AGCAAGCGAG GTTCGACCCG ACACACGTGC

1401  AACCCCCCGT TCAGCCCGAC CGCTGCGCCT TATCCGGTAA CTATCGTCTT
      TTGGGGGGCA AGTCGGGCTG GCGACGCGGA ATAGGCCATT GATAGCAGAA

1451  GAGTCCAACC CGGTAAGACA CGACTTATCG CCACTGGCAG CAGCCACTGG
      CTCAGGTTGG GCCATTCTGT GCTGAATAGC GGTGACCGTC GTCGGTGACC

1501  TAACAGGATT AGCAGAGCGA GGTATGTAGG CGGTGCTACA GAGTTCTTGA
      ATTGTCCTAA TCGTCTCGCT CCATACATCC GCCACGATGT CTCAAGAACT

1551  AGTGGTGGCC TAACTACGGC TACACTAGAA GAACAGTATT TGGTATCTGC
      TCACCACCGG ATTGATGCCG ATGTGATCTT CTTGTCATAA ACCATAGACG

1601  GCTCTGCTGT AGCCAGTTAC CTTCGGAAAA AGAGTTGGTA GCTCTTGATC
      CGAGACGACA TCGGTCAATG GAAGCCTTTT TCTCAACCAT CGAGAACTAG

1651  CGGCAAACAA ACCACCGCTG GTAGCGGTGG TTTTTTTGTT TGCAAGCAGC
      GCCGTTTGTT TGGTGGCGAC CATCGCCACC AAAAAAACAA ACGTTCGTCG

1701  AGATTACGCG CAGAAAAAAA GGATCTCAAG AAGATCCTTT GATCTTTTCT
      TCTAATGCGC GTCTTTTTTT CCTAGAGTTC TTCTAGGAAA CTAGAAAAGA
```

Figure 35: functional map and sequence of modular vector pCAL4 (continued)

```
1751   ACGGGGTCTG ACGCTCAGTG GAACGAAAAC TCACGTTAAG GGATTTTGGT
       TGCCCCAGAC TGCGAGTCAC CTTGCTTTTG AGTGCAATTC CCTAAAACCA

        BglII
       ~~~~~~~
1801   CAGATCTAGC ACCAGGCGTT TAAGGGCACC AATAACTGCC TTAAAAAAAT
       GTCTAGATCG TGGTCCGCAA ATTCCCGTGG TTATTGACGG AATTTTTTTA

1851   TACGCCCCGC CCTGCCACTC ATCGCAGTAC TGTTGTAATT CATTAAGCAT
       ATGCGGGGCG GGACGGTGAG TAGCGTCATG ACAACATTAA GTAATTCGTA

1901   TCTGCCGACA TGGAAGCCAT CACAAACGGC ATGATGAACC TGAATCGCCA
       AGACGGCTGT ACCTTCGGTA GTGTTTGCCG TACTACTTGG ACTTAGCGGT

1951   GCGGCATCAG CACCTTGTCG CCTTGCGTAT AATATTTGCC CATAGTGAAA
       CGCCGTAGTC GTGGAACAGC GGAACGCATA TTATAAACGG GTATCACTTT

2001   ACGGGGGCGA AGAAGTTGTC CATATTGGCT ACGTTTAAAT CAAAACTGGT
       TGCCCCCGCT TCTTCAACAG GTATAACCGA TGCAAATTTA GTTTTGACCA

2051   GAAACTCACC CAGGGATTGG CTGAGACGAA AAACATATTC TCAATAAACC
       CTTTGAGTGG GTCCCTAACC GACTCTGCTT TTTGTATAAG AGTTATTTGG
```

Figure 35: functional map and sequence of modular vector pCAL4 (continued)

```
2101   CTTTAGGGAA ATAGGCCAGG TTTTCACCGT AACACGCCAC ATCTTGCGAA
       GAAATCCCTT TATCCGGTCC AAAAGTGGCA TTGTGCGGTG TAGAACGCTT

2151   TATATGTGTA GAAACTGCCG GAAATCGTCG TGGTATTCAC TCCAGAGCGA
       ATATACACAT CTTTGACGGC CTTTAGCAGC ACCATAAGTG AGGTCTCGCT

2201   TGAAAACGTT TCAGTTTGCT CATGGAAAAC GGTGTAACAA GGGTGAACAC
       ACTTTTGCAA AGTCAAACGA GTACCTTTTG CCACATTGTT CCCACTTGTG

2251   TATCCCATAT CACCAGCTCA CCGTCTTTCA TTGCCATACG GAACTCCGGG
       ATAGGGTATA GTGGTCGAGT GGCAGAAAGT AACGGTATGC CTTGAGGCCC

2301   TGAGCATTCA TCAGGCGGGC AAGAATGTGA ATAAAGGCCG GATAAAACTT
       ACTCGTAAGT AGTCCGCCCG TTCTTACACT TATTTCCGGC CTATTTTGAA

2351   GTGCTTATTT TTCTTTACGG TCTTTAAAAA GGCCGTAATA TCCAGCTGAA
       CACGAATAAA AAGAAATGCC AGAAATTTTT CCGGCATTAT AGGTCGACTT

2401   CGGTCTGGTT ATAGGTACAT TGAGCAACTG ACTGAAATGC CTCAAAATGT
       GCCAGACCAA TATCCATGTA ACTCGTTGAC TGACTTTACG GAGTTTTACA

2451   TCTTTACGAT GCCATTGGGA TATATCAACG GTGGTATATC CAGTGATTTT
       AGAAATGCTA CGGTAACCCT ATATAGTTGC CACCATATAG GTCACTAAAA
```

Figure 35: functional map and sequence of modular vector pCAL4 (continued)

```
2501   TTTCTCCATT TTAGCTTCCT TAGCTCCTGA AAATCTCGAT AACTCAAAAA
       AAAGAGGTAA AATCGAAGGA ATCGAGGACT TTTAGAGCTA TTGAGTTTTT

2551   ATACGCCCGG TAGTGATCTT ATTTCATTAT GGTGAAAGTT GGAACCTCAC
       TATGCGGGCC ATCACTAGAA TAAAGTAATA CCACTTTCAA CCTTGGAGTG

         AatII
        ~~~~~~~
2601   CCGACGTCTA ATGTGAGTTA GCTCACTCAT TAGGCACCCC AGGCTTTACA
       GGCTGCAGAT TACACTCAAT CGAGTGAGTA ATCCGTGGGG TCCGAAATGT

2651   CTTTATGCTT CCGGCTCGTA TGTTGTGTGG AATTGTGAGC GGATAACAAT
       GAAATACGAA GGCCGAGCAT ACAACACACC TTAACACTCG CCTATTGTTA

                                               XbaI    SphI
                                             ~~~~~~~~~~~~~~~
2701   TTCACACAGG AAACAGCTAT GACCATGATT ACGAATTTCT AGAGCATGCG
       AAGTGTGTCC TTTGTCGATA CTGGTACTAA TGCTTAAAGA TCTCGTACGC

       EcoRI

2751   GGGGG
       CCCCC
```

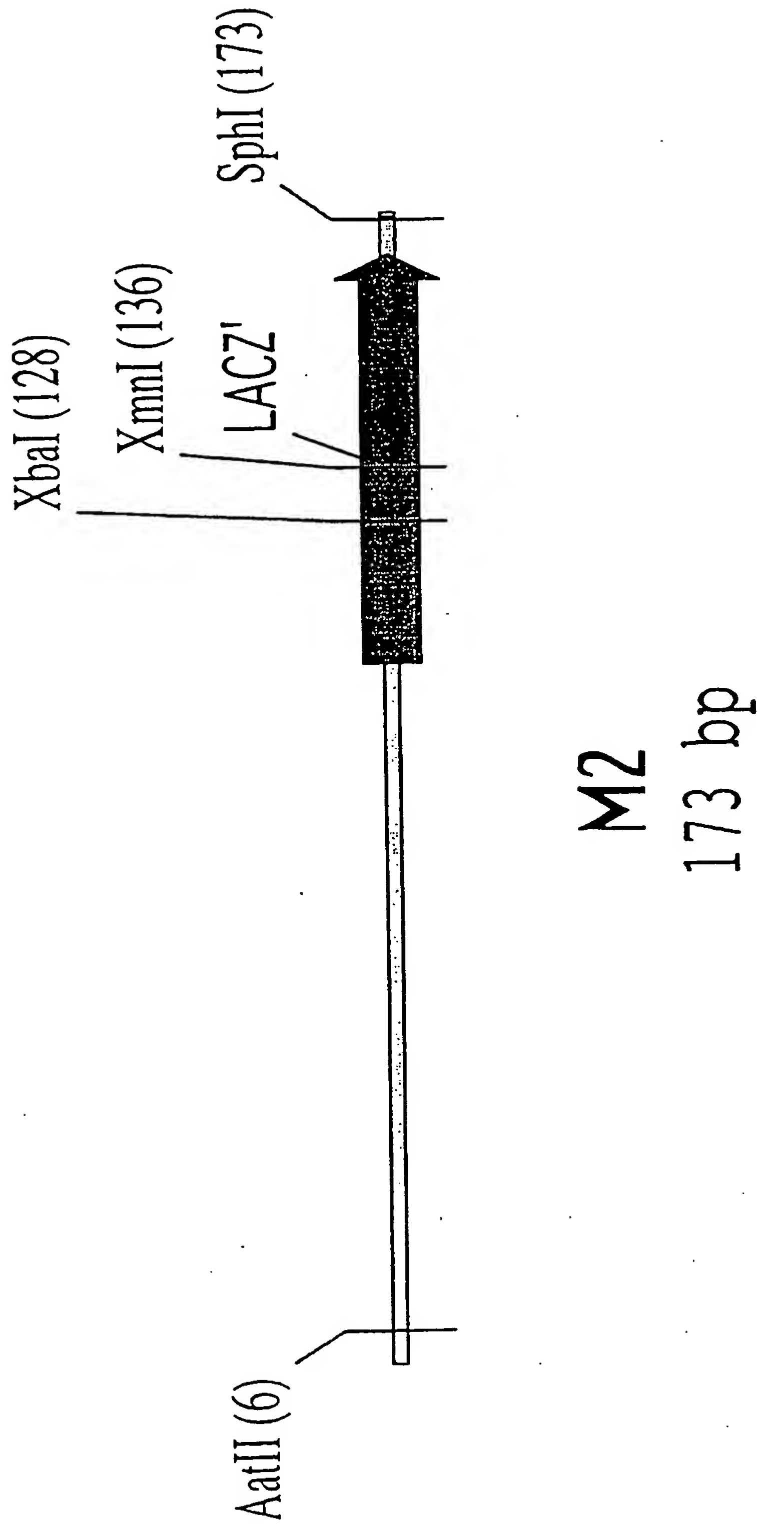


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 2:

```
       AatII
       ~~~~~~
  1    GACGTCTTAA TGTGAGTTAG CTCACTCATT AGGCACCCCA GGCTTTACAC
       CTGCAGAATT ACACTCAATC GAGTGAGTAA TCCGTGGGGT CCGAAATGTG

 51    TTTATGCTTC CGGCTCGTAT GTTGTGTGGA ATTGTGAGCG GATAACAATT
       AAATACGAAG GCCGAGCATA CAACACACCT TAACACTCGC CTATTGTTAA

                                           XmnI
                                       ~~~~~~~~~~~
                                 XbaI
                               ~~~~~~~~
101    TCACACAGGA AACAGCTATG ACCATGTCTA GAATAACTTC GTATAATGTA
       AGTGTGTCCT TTGTCGATAC TGGTACAGAT CTTATTGAAG CATATTACAT

                        SphI
                      ~~~~~~
151    CGCTATACGA AGTTATCGCA TGC
       GCGATATGCT TCAATAGCGT ACG
```

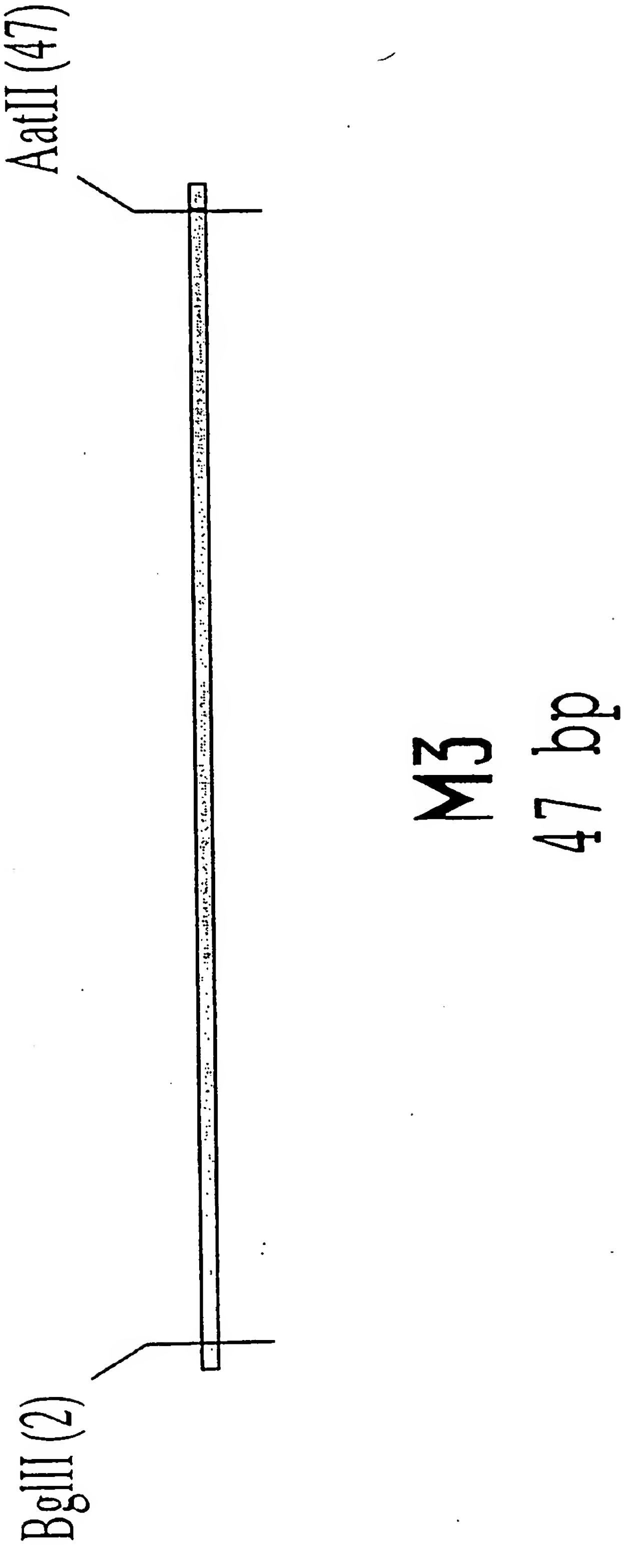


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 3:

```
    BglII                                             AatII
    ~~~~~~                                            ~~~~~~
1   AGATCTCATA ACTTCGTATA ATGTATGCTA TACGAAGTTA TGACGTC
    TCTAGAGTAT TGAAGCATAT TACATACGAT ATGCTTCAAT ACTGCAG
```

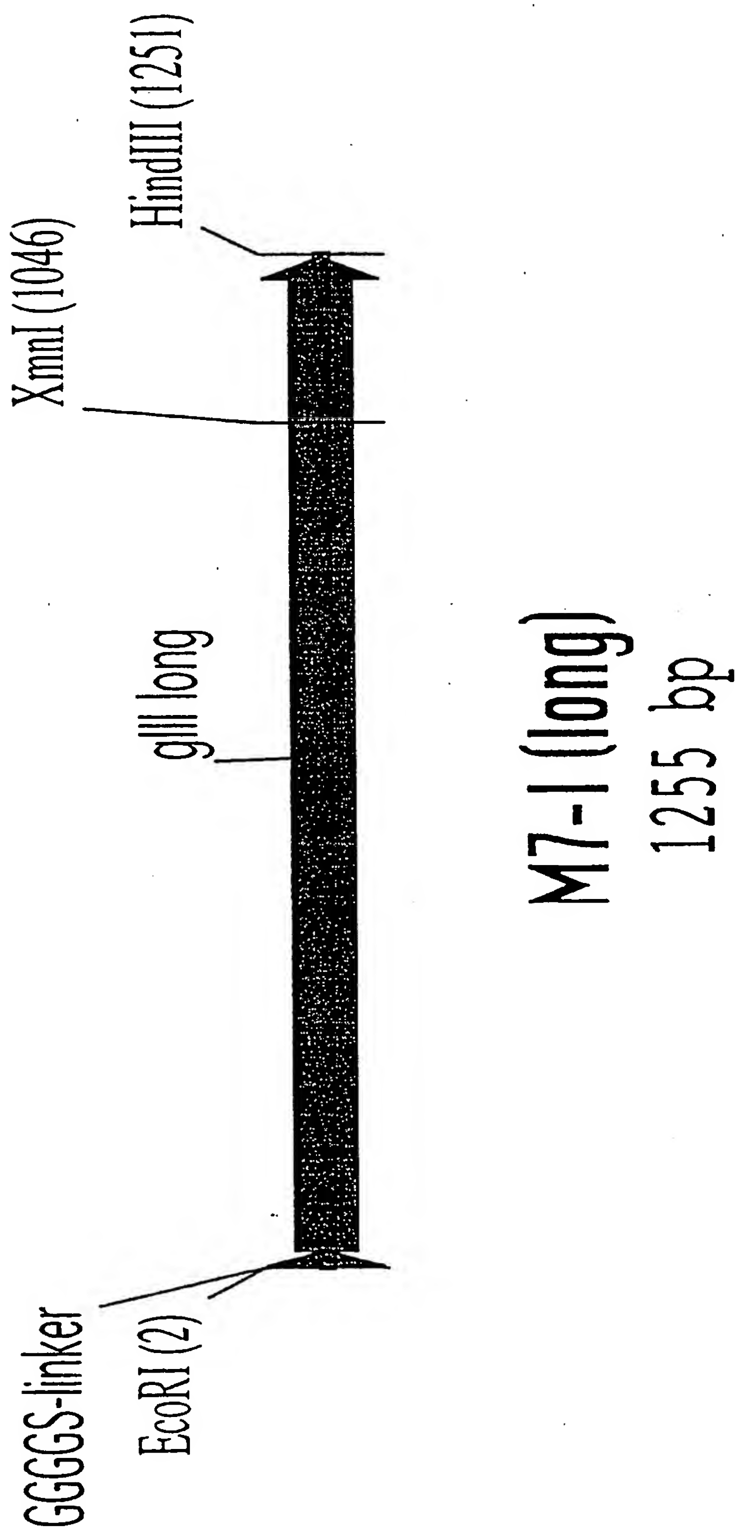


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 7-I (long):

```
          EcoRI
          ~~~~~~~
  1       GAATTCGGTG GTGGTGGATC TGCGTGCGCT GAAACGGTTG AAAGTTGTTT
          CTTAAGCCAC CACCACCTAG ACGCACGCGA CTTTGCCAAC TTTCAACAAA

 51       AGCAAAATCC CATACAGAAA ATTCATTTAC TAACGTCTGG AAAGACGACA
          TCGTTTTAGG GTATGTCTTT TAAGTAAATG ATTGCAGACC TTTCTGCTGT

101       AAACTTTAGA TCGTTACGCT AACTATGAGG GCTGTCTGTG GAATGCTACA
          TTTGAAATCT AGCAATGCGA TTGATACTCC CGACAGACAC CTTACGATGT

151       GGCGTTGTAG TTTGTACTGG TGACGAAACT CAGTGTTACG GTACATGGGT
          CCGCAACATC AAACATGACC ACTGCTTTGA GTCACAATGC CATGTACCCA

201       TCCTATTGGG CTTGCTATCC CTGAAAATGA GGGTGGTGGC TCTGAGGGTG
          AGGATAACCC GAACGATAGG GACTTTTACT CCCACCACCG AGACTCCCAC

251       GCGGTTCTGA GGGTGGCGGT TCTGAGGGTG GCGGTACTAA ACCTCCTGAG
          CGCCAAGACT CCCACCGCCA AGACTCCCAC CGCCATGATT TGGAGGACTC

301       TACGGTGATA CACCTATTCC GGGCTATACT TATATCAACC CTCTCGACGG
          ATGCCACTAT GTGGATAAGG CCCGATATGA ATATAGTTGG GAGAGCTGCC
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
351  CACTTATCCG CCTGGTACTG AGCAAAACCC CGCTAATCCT AATCCTTCTC
     GTGAATAGGC GGACCATGAC TCGTTTTGGG GCGATTAGGA TTAGGAAGAG

401  TTGAGGAGTC TCAGCCTCTT AATACTTTCA TGTTTCAGAA TAATAGGTTC
     AACTCCTCAG AGTCGGAGAA TTATGAAAGT ACAAAGTCTT ATTATCCAAG

451  CGAAATAGGC AGGGGGCATT AACTGTTTAT ACGGGCACTG TTACTCAAGG
     GCTTTATCCG TCCCCCGTAA TTGACAAATA TGCCCGTGAC AATGAGTTCC

501  CACTGACCCC GTTAAAACTT ATTACCAGTA CACTCCTGTA TCATCAAAAG
     GTGACTGGGG CAATTTTGAA TAATGGTCAT GTGAGGACAT AGTAGTTTTC

551  CCATGTATGA CGCTTACTGG AACGGTAAAT TCAGAGACTG CGCTTTCCAT
     GGTACATACT GCGAATGACC TTGCCATTTA AGTCTCTGAC GCGAAAGGTA

601  TCTGGCTTTA ATGAGGATTT ATTTGTTTGT GAATATCAAG GCCAATCGTC
     AGACCGAAAT TACTCCTAAA TAAACAAACA CTTATAGTTC CGGTTAGCAG

651  TGACCTGCCT CAACCTCCTG TCAATGCTGG CGGCGGCTCT GGTGGTGGTT
     ACTGGACGGA GTTGGAGGAC AGTTACGACC GCCGCCGAGA CCACCACCAA

701  CTGGTGGCGG CTCTGAGGGT GGTGGCTCTG AGGGTGGCGG TTCTGAGGGT
     GACCACCGCC GAGACTCCCA CCACCGAGAC TCCCACCGCC AAGACTCCCA
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
751   GGCGGCTCTG AGGGAGGCGG TTCCGGTGGT GGCTCTGGTT CCGGTGATTT
      CCGCCGAGAC TCCCTCCGCC AAGGCCACCA CCGAGACCAA GGCCACTAAA

801   TGATTATGAA AAGATGGCAA ACGCTAATAA GGGGGCTATG ACCGAAAATG
      ACTAATACTT TTCTACCGTT TGCGATTATT CCCCCGATAC TGGCTTTTAC

851   CCGATGAAAA CGCGCTACAG TCTGACGCTA AAGGCAAACT TGATTCTGTC
      GGCTACTTTT GCGCGATGTC AGACTGCGAT TTCCGTTTGA ACTAAGACAG

901   GCTACTGATT ACGGTGCTGC TATCGATGGT TTCATTGGTG ACGTTTCCGG
      CGATGACTAA TGCCACGACG ATAGCTACCA AAGTAACCAC TGCAAAGGCC

951   CCTTGCTAAT GGTAATGGTG CTACTGGTGA TTTTGCTGGC TCTAATTCCC
      GGAACGATTA CCATTACCAC GATGACCACT AAAACGACCG AGATTAAGGG

                                                  XmnI
                                               ~~~~~~~~~~~
1001  AAATGGCTCA AGTCGGTGAA GGTGATAATT CACCTTTAAT GAATAATTTC
      TTTACCGAGT TCAGCCACTT CCACTATTAA GTGGAAATTA CTTATTAAAG

1051  CGTCAATATT TACCTTCCAT CCCTCAATCG GTTGAATGTC GCCCTTTTGT
      GCAGTTATAA ATGGAAGGTA GGGAGTTAGC CAACTTACAG CGGGAAAACA
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
1101   CTTTGGCGCT GGTAAACCCT ATGAATTTTC TATTGATTGT GACAAAATAA
       GAAACCGCGA CCATTTGGGA TACTTAAAAG ATAACTAACA CTGTTTTATT

1151   ACTTATTCCG TGGTGTCTTT GCGTTTCTTT TATATGTTGC CACCTTTATG
       TGAATAAGGC ACCACAGAAA CGCAAAGAAA ATATACAACG GTGGAAATAC

                                                     HindIII
                                                           ~
1201   TATGTATTTT CTACGTTTGC TAACATACTG CGTAATAAGG AGTCTTGATA
       ATACATAAAA GATGCAAACG ATTGTATGAC GCATTATTCC TCAGAACTAT

       HindI
       ~~~~
1251   AGCTT
       TCGAA
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vector (continued)

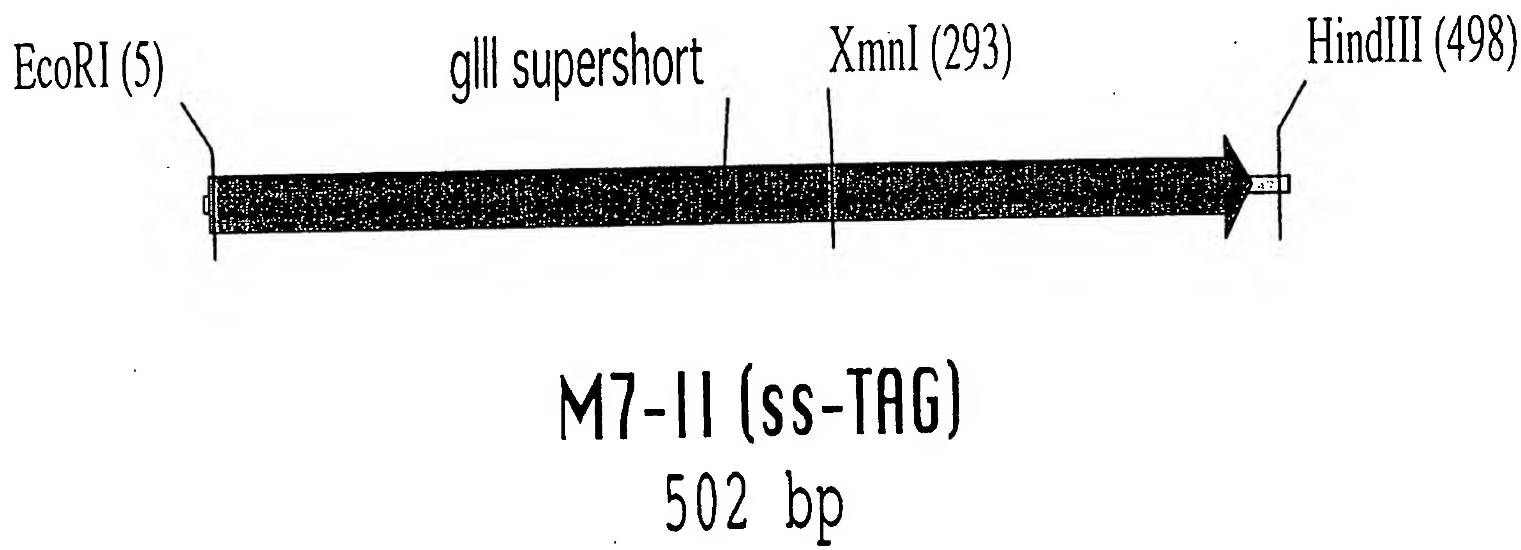


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 7-II (ss-TAG):

```
        EcoRI
       ~~~~~~~
  1   CGGGAATTCG GAGGCGGTTC CGGTGGTGGC TCTGGTTCCG GTGATTTTGA
      GCCCTTAAGC CTCCGCCAAG GCCACCACCG AGACCAAGGC CACTAAAACT

 51   TTATGAAAAG ATGGCAAACG CTAATAAGGG GGCTATGACC GAAAATGCCG
      AATACTTTTC TACCGTTTGC GATTATTCCC CCGATACTGG CTTTTACGGC

101   ATGAAAACGC GCTACAGTCT GACGCTAAAG GCAAACTTGA TTCTGTCGCT
      TACTTTTGCG CGATGTCAGA CTGCGATTTC CGTTTGAACT AAGACAGCGA

151   ACTGATTACG GTGCTGCTAT CGATGGTTTC ATTGGTGACG TTTCCGGCCT
      TGACTAATGC CACGACGATA GCTACCAAAG TAACCACTGC AAAGGCCGGA

201   TGCTAATGGT AATGGTGCTA CTGGTGATTT TGCTGGCTCT AATTCCCAAA
      ACGATTACCA TTACCACGAT GACCACTAAA ACGACCGAGA TTAAGGGTTT

                                                 XmnI
                                             ~~~~~~~~~~~~
251   TGGCTCAAGT CGGTGACGGT GATAATTCAC CTTTAATGAA TAATTTCCGT
      ACCGAGTTCA GCCACTGCCA CTATTAAGTG GAAATTACTT ATTAAAGGCA
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
301   CAATATTTAC CTTCCCTCCC TCAATCGGTT GAATGTCGCC CTTTTGTCTT
      GTTATAAATG GAAGGGAGGG AGTTAGCCAA CTTACAGCGG GAAAACAGAA

351   TGGCGCTGGT AAACCATATG AATTTTCTAT TGATTGTGAC AAAATAAACT
      ACCGCGACCA TTTGGTATAC TTAAAAGATA ACTAACACTG TTTTATTTGA

401   TATTCCGTGG TGTCTTTGCG TTTCTTTTAT ATGTTGCCAC CTTTATGTAT
      ATAAGGCACC ACAGAAACGC AAAGAAAATA TACAACGGTG GAAATACATA

                                                   HindIII
                                                      ~~~~
451   GTATTTTCTA CGTTTGCTAA CATACTGCGT AATAAGGAGT CTTGATAAGC
      CATAAAAGAT GCAAACGATT GTATGACGCA TTATTCCTCA GAACTATTCG

      Hi
      ~
501   TT
      AA
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

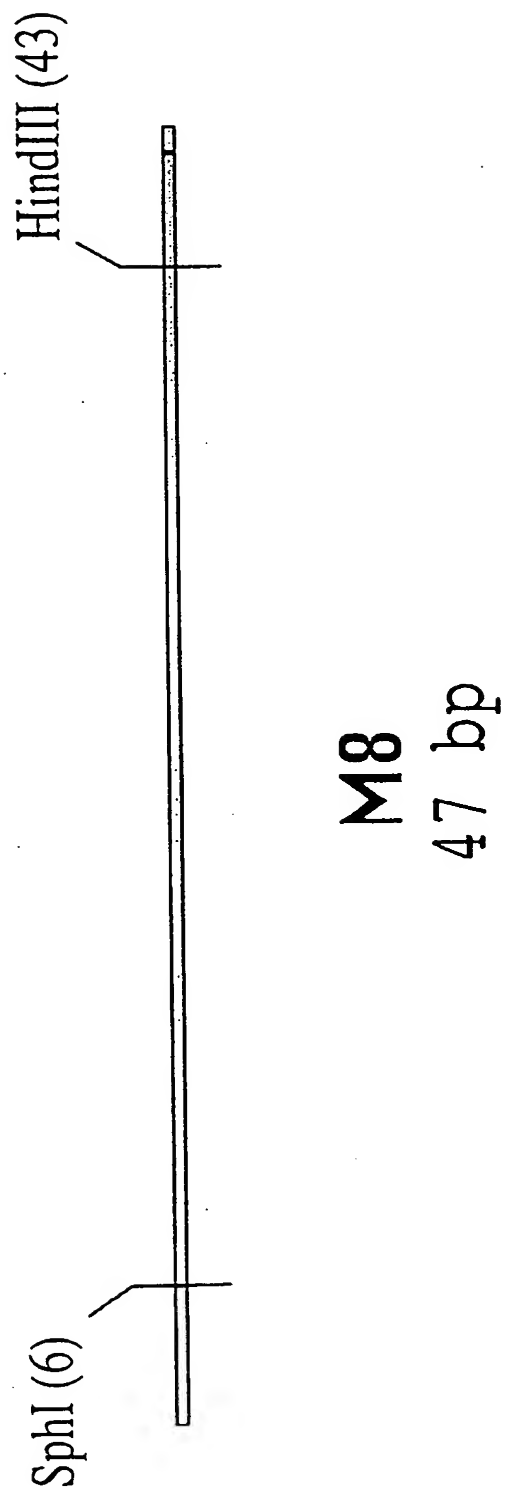


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
M 8:

     SphI                                                  HindIII
    ~~~~~~                                                  ~~~~~~
1   GCATGCCATA ACTTCGTATA ATGTACGCTA TACGAAGTTA TAAGCTT
    CGTACGGTAT TGAAGCATAT TACATGCGAT ATGCTTCAAT ATTCGAA
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

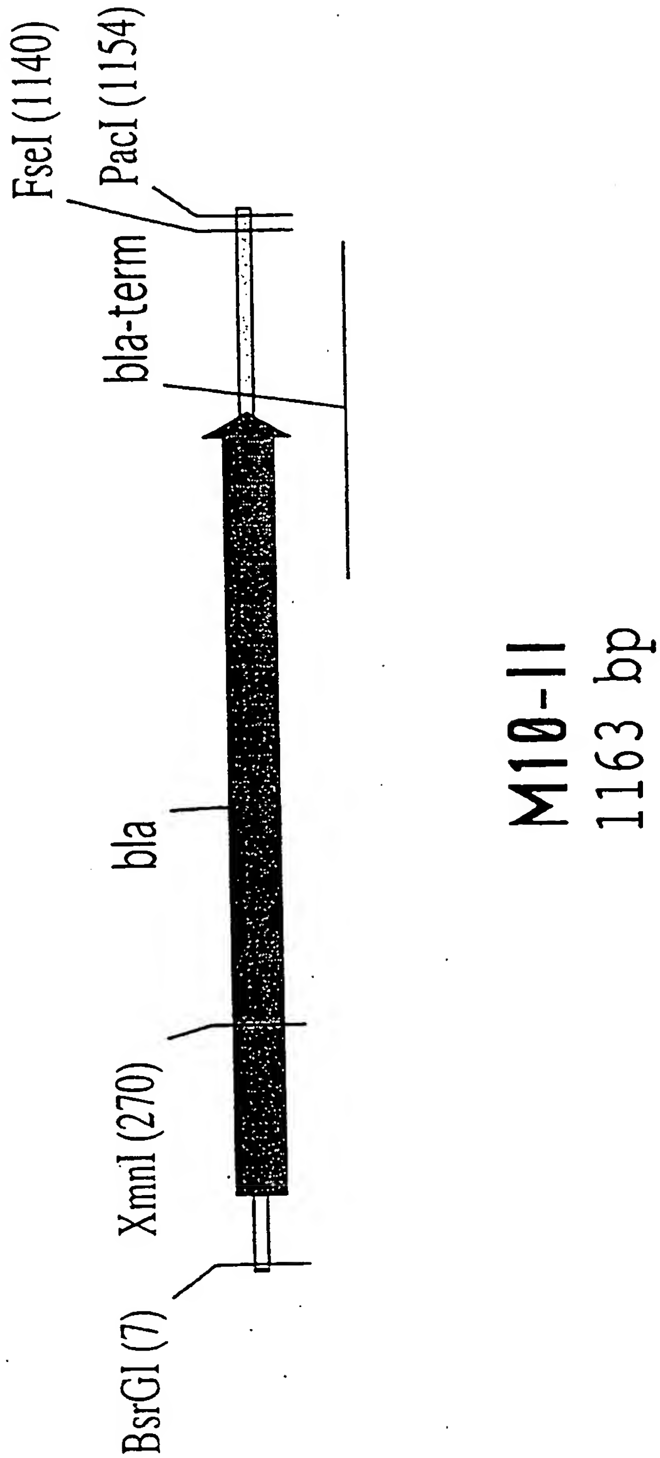


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 10-II:

```
                BsrGI
                ~~~~~~~~
  1   GGGGGTGTAC ATTCAAATAT GTATCCGCTC ATGAGACAAT AACCCTGATA
      CCCCCACATG TAAGTTTATA CATAGGCGAG TACTCTGTTA TTGGGACTAT

 51   AATGCTTCAA TAATATTGAA AAAGGAAGAG TATGAGTATT CAACATTTCC
      TTACGAAGTT ATTATAACTT TTTCCTTCTC ATACTCATAA GTTGTAAAGG

101   GTGTCGCCCT TATTCCCTTT TTTGCGGCAT TTTGCCTTCC TGTTTTTGCT
      CACAGCGGGA ATAAGGGAAA AAACGCCGTA AAACGGAAGG ACAAAAACGA

151   CACCCAGAAA CGCTGGTGAA AGTAAAAGAT GCTGAGGATC AGTTGGGTGC
      GTGGGTCTTT GCGACCACTT TCATTTTCTA CGACTCCTAG TCAACCCACG

201   GCGAGTGGGT TACATCGAAC TGGATCTCAA CAGCGGTAAG ATCCTTGAGA
      CGCTCACCCA ATGTAGCTTG ACCTAGAGTT GTCGCCATTC TAGGAACTCT

                           XmnI
                      ~~~~~~~~~~~~
251   GTTTTCGCCC CGAAGAACGT TTTCCAATGA TGAGCACTTT TAAAGTTCTG
      CAAAAGCGGG GCTTCTTGCA AAAGGTTACT ACTCGTGAAA ATTTCAAGAC
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
301   CTATGTGGCG CGGTATTATC CCGTATTGAC GCCGGGCAAG AGCAACTCGG
      GATACACCGC GCCATAATAG GGCATAACTG CGGCCCGTTC TCGTTGAGCC

351   TCGCCGCATA CACTATTCTC AGAATGACTT GGTTGAGTAC TCACCAGTCA
      AGCGGCGTAT GTGATAAGAG TCTTACTGAA CCAACTCATG AGTGGTCAGT

401   CAGAAAAGCA TCTTACGGAT GGCATGACAG TAAGAGAATT ATGCAGTGCT
      GTCTTTTCGT AGAATGCCTA CCGTACTGTC ATTCTCTTAA TACGTCACGA

451   GCCATAACCA TGAGTGATAA CACTGCGGCC AACTTACTTC TGACAACGAT
      CGGTATTGGT ACTCACTATT GTGACGCCGG TTGAATGAAG ACTGTTGCTA

501   CGGAGGACCG AAGGAGCTAA CCGCTTTTTT GCACAACATG GGGGATCATG
      GCCTCCTGGC TTCCTCGATT GGCGAAAAAA CGTGTTGTAC CCCCTAGTAC

551   TAACTCGCCT TGATCGTTGG GAACCGGAGC TGAATGAAGC CATACCAAAC
      ATTGAGCGGA ACTAGCAACC CTTGGCCTCG ACTTACTTCG GTATGGTTTG

601   GACGAGCGTG ACACCACGAT GCCTGTAGCA ATGGCAACAA CGTTGCGCAA
      CTGCTCGCAC TGTGGTGCTA CGGACATCGT TACCGTTGTT GCAACGCGTT

651   ACTATTAACT GGCGAACTAC TTACTCTAGC TTCCCGGCAA CAGTTAATAG
      TGATAATTGA CCGCTTGATG AATGAGATCG AAGGGCCGTT GTCAATTATC
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
701   ACTGGATGGA GGCGGATAAA GTTGCAGGAC CACTTCTGCG CTCGGCCCTT
      TGACCTACCT CCGCCTATTT CAACGTCCTG GTGAAGACGC GAGCCGGGAA

751   CCGGCTGGCT GGTTTATTGC TGATAAATCT GGAGCCGGTG AGCGTGGGTC
      GGCCGACCGA CCAAATAACG ACTATTTAGA CCTCGGCCAC TCGCACCCAG

801   TCGCGGTATC ATTGCAGCAC TGGGGCCAGA TGGTAAGCCC TCCCGTATCG
      AGCGCCATAG TAACGTCGTG ACCCCGGTCT ACCATTCGGG AGGGCATAGC

851   TAGTTATCTA CACGACGGGG AGTCAGGCAA CTATGGATGA ACGAAATAGA
      ATCAATAGAT GTGCTGCCCC TCAGTCCGTT GATACCTACT TGCTTTATCT

901   CAGATCGCTG AGATAGGTGC CTCACTGATT AAGCATTGGG TAACTGTCAG
      GTCTAGCGAC TCTATCCACG GAGTGACTAA TTCGTAACCC ATTGACAGTC

951   ACCAAGTTTA CTCATATATA CTTTAGATTG ATTTAAAACT TCATTTTTAA
      TGGTTCAAAT GAGTATATAT GAAATCTAAC TAAATTTTGA AGTAAAAATT

1001  TTTAAAAGGA TCTAGGTGAA GATCCTTTTT GATAATCTCA TGACCAAAAT
      AAATTTTCCT AGATCCACTT CTAGGAAAAA CTATTAGAGT ACTGGTTTTA

1051  CCCTTAACGT GAGTTTTCGT TCCACTGAGC GTCAGACCCC GTAGAAAAGA
      GGGAATTGCA CTCAAAAGCA AGGTGACTCG CAGTCTGGGG CATCTTTTCT
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
                                           FseI        PacI
                                         ~~~~~~~~~      ~~
1101  TCAAAGGATC TTCTTGAGAT CCTTTTTGAT AATGGCCGGC CCCCCCCCTT
      AGTTTCCTAG AAGAACTCTA GGAAAAACTA TTACCGGCCG GGGGGGGGAA

      PacI
      ~~~~~~
1151  AATTAAGGGG GGG
      TTAATTCCCC CCC
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

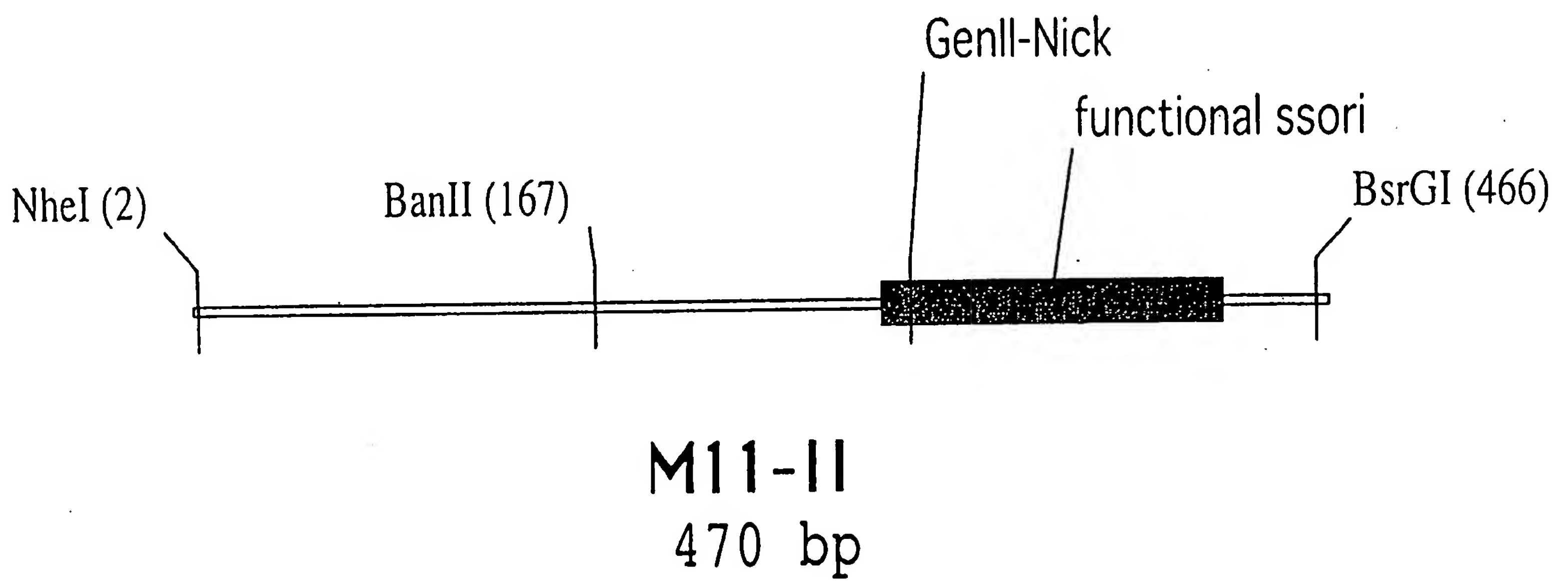


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M11-II:

```
          NheI
         ~~~~~~~
  1      GCTAGCACGC GCCCTGTAGC GGCGCATTAA GCGCGGCGGG TGTGGTGGTT
         CGATCGTGCG CGGGACATCG CCGCGTAATT CGCGCCGCCC ACACCACCAA

 51      ACGCGCAGCG TGACCGCTAC ACTTGCCAGC GCCCTAGCGC CCGCTCCTTT
         TGCGCGTCGC ACTGGCGATG TGAACGGTCG CGGGATCGCG GGCGAGGAAA

101      CGCTTTCTTC CCTTCCTTTC TCGCCACGTT CGCCGGCTTT CCCCGTCAAG
         GCGAAAGAAG GGAAGGAAAG AGCGGTGCAA GCGGCCGAAA GGGGCAGTTC

                     BanII
                    ~~~~~~~
151      CTCTAAATCG GGGGCTCCCT TTAGGGTTCC GATTTAGTGC TTTACGGCAC
         GAGATTTAGC CCCCGAGGGA AATCCCAAGG CTAAATCACG AAATGCCGTG

201      CTCGACCCCA AAAAACTTGA TTAGGGTGAT GGTTCTCGTA GTGGGCCATC
         GAGCTGGGGT TTTTTGAACT AATCCCACTA CCAAGAGCAT CACCCGGTAG

251      GCCCTGATAG ACGGTTTTTC GCCCTTTGAC GTTGGAGTCC ACGTTCTTTA
         CGGGACTATC TGCCAAAAAG CGGGAAACTG CAACCTCAGG TGCAAGAAAT
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
301   ATAGTGGACT CTTGTTCCAA ACTGGAACAA CACTCAACCC TATCTCGGTC
      TATCACCTGA GAACAAGGTT TGACCTTGTT GTGAGTTGGG ATAGAGCCAG

351   TATTCTTTTG ATTTATAAGG GATTTTGCCG ATTTCGGCCT ATTGGTTAAA
      ATAAGAAAAC TAAATATTCC CTAAAACGGC TAAAGCCGGA TAACCAATTT

401   AAATGAGCTG ATTTAACAAA AATTTAACGC GAATTTTAAC AAAATATTAA
      TTTACTCGAC TAAATTGTTT TTAAATTGCG CTTAAAATTG TTTTATAATT

                          BsrGI
                        ~~~~~~~
451   CGTTTACAAT TTCATGTACA
      GCAAATGTTA AAGTACATGT
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

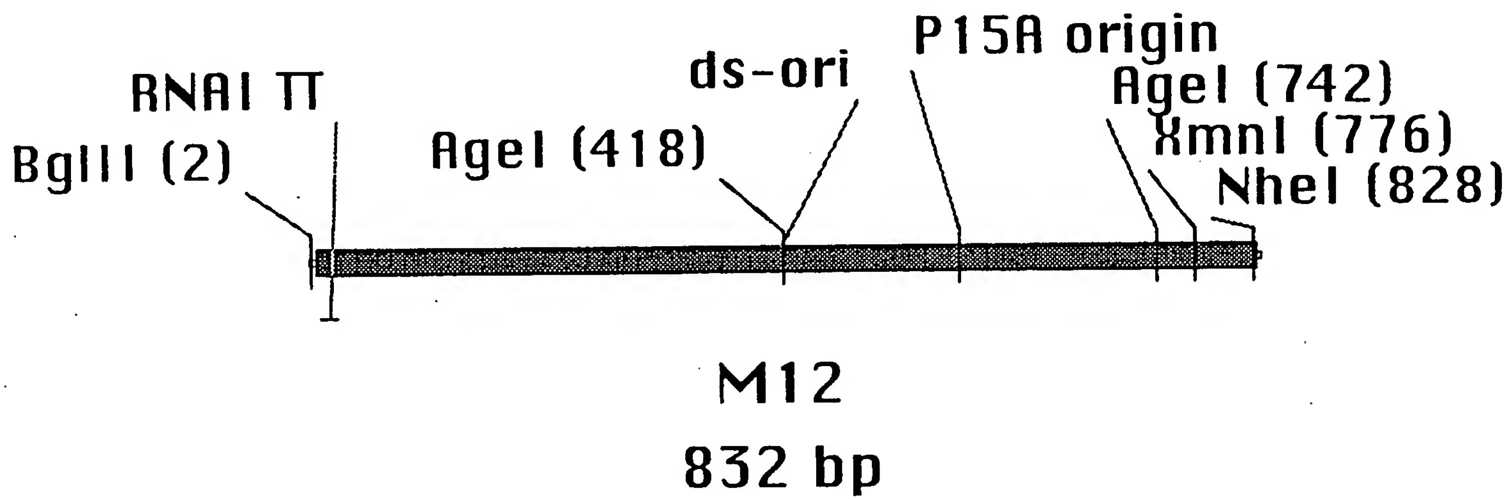


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
M  12:
      BglII
      ~~~~~~
  1   AGATCTAATA AGATGATCTT CTTGAGATCG TTTTGGTCTG CGCGTAATCT
      TCTAGATTAT TCTACTAGAA GAACTCTAGC AAAACCAGAC GCGCATTAGA

 51   CTTGCTCTGA AAACGAAAAA ACCGCCTTGC AGGGCGGTTT TTCGTAGGTT
      GAACGAGACT TTTGCTTTTT TGGCGGAACG TCCCGCCAAA AAGCATCCAA

101   CTCTGAGCTA CCAACTCTTT GAACCGAGGT AACTGGCTTG GAGGAGCGCA
      GAGACTCGAT GGTTGAGAAA CTTGGCTCCA TTGACCGAAC CTCCTCGCGT

151   GTCACTAAAA CTTGTCCTTT CAGTTTAGCC TTAACCGGCG CATGACTTCA
      CAGTGATTTT GAACAGGAAA GTCAAATCGG AATTGGCCGC GTACTGAAGT

201   AGACTAACTC CTCTAAATCA ATTACCAGTG GCTGCTGCCA GTGGTGCTTT
      TCTGATTGAG GAGATTTAGT TAATGGTCAC CGACGACGGT CACCACGAAA

251   TGCATGTCTT TCCGGGTTGG ACTCAAGACG ATAGTTACCG GATAAGGCGC
      ACGTACAGAA AGGCCCAACC TGAGTTCTGC TATCAATGGC CTATTCCGCG

301   AGCGGTCGGA CTGAACGGGG GGTTCGTGCA TACAGTCCAG CTTGGAGCGA
      TCGCCAGCCT GACTTGCCCC CCAAGCACGT ATGTCAGGTC GAACCTCGCT
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
351   ACTGCCTACC CGGAACTGAG TGTCAGGCGT GGAATGAGAC AAACGCGGCC
      TGACGGATGG GCCTTGACTC ACAGTCCGCA CCTTACTCTG TTTGCGCCGG

                           AgeI
                         ~~~~~~~~
401   ATAACAGCGG AATGACACCG GTAAACCGAA AGGCAGGAAC AGGAGAGCGC
      TATTGTCGCC TTACTGTGGC CATTTGGCTT TCCGTCCTTG TCCTCTCGCG

451   AGGAGGGAGC CGCCAGGGGG AAACGCCTGG TATCTTTATA GTCCTGTCGG
      TCCTCCCTCG GCGGTCCCCC TTTGCGGACC ATAGAAATAT CAGGACAGCC

501   GTTTCGCCAC CACTGATTTG AGCGTCAGAT TTCGTGATGC TTGTCAGGGG
      CAAAGCGGTG GTGACTAAAC TCGCAGTCTA AAGCACTACG AACAGTCCCC

551   GGCGGAGCCT ATGGAAAAAC GGCTTTGCCG CGGCCCTCTC ACTTCCCTGT
      CCGCCTCGGA TACCTTTTTG CCGAAACGGC GCCGGGAGAG TGAAGGGACA

601   TAAGTATCTT CCTGGCATCT TCCAGGAAAT CTCCGCCCCG TTCGTAAGCC
      ATTCATAGAA GGACCGTAGA AGGTCCTTTA GAGGCGGGGC AAGCATTCGG

651   ATTTCCGCTC GCCGCAGTCG AACGACCGAG CGTAGCGAGT CAGTGAGCGA
      TAAAGGCGAG CGGCGTCAGC TTGCTGGCTC GCATCGCTCA GTCACTCGCT
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
                                                      AgeI
                                                      ~~~~~~~
701  GGAAGCGGAA TATATCCTGT ATCACATATT CTGCTGACGC ACCGGTGCAG
     CCTTCGCCTT ATATAGGACA TAGTGTATAA GACGACTGCG TGGCCACGTC

                                  XmnI
                           ~~~~~~~~~~~~
751  CCTTTTTTCT CCTGCCACAT GAAGCACTTC ACTGACACCC TCATCAGTGC
     GGAAAAAAGA GGACGGTGTA CTTCGTGAAG TGACTGTGGG AGTAGTCACG

                                      NheI
                                    ~~~~~~~
801  CAACATAGTA AGCCAGTATA CACTCCGCTA GC
     GTTGTATCAT TCGGTCATAT GTGAGGCGAT CG
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

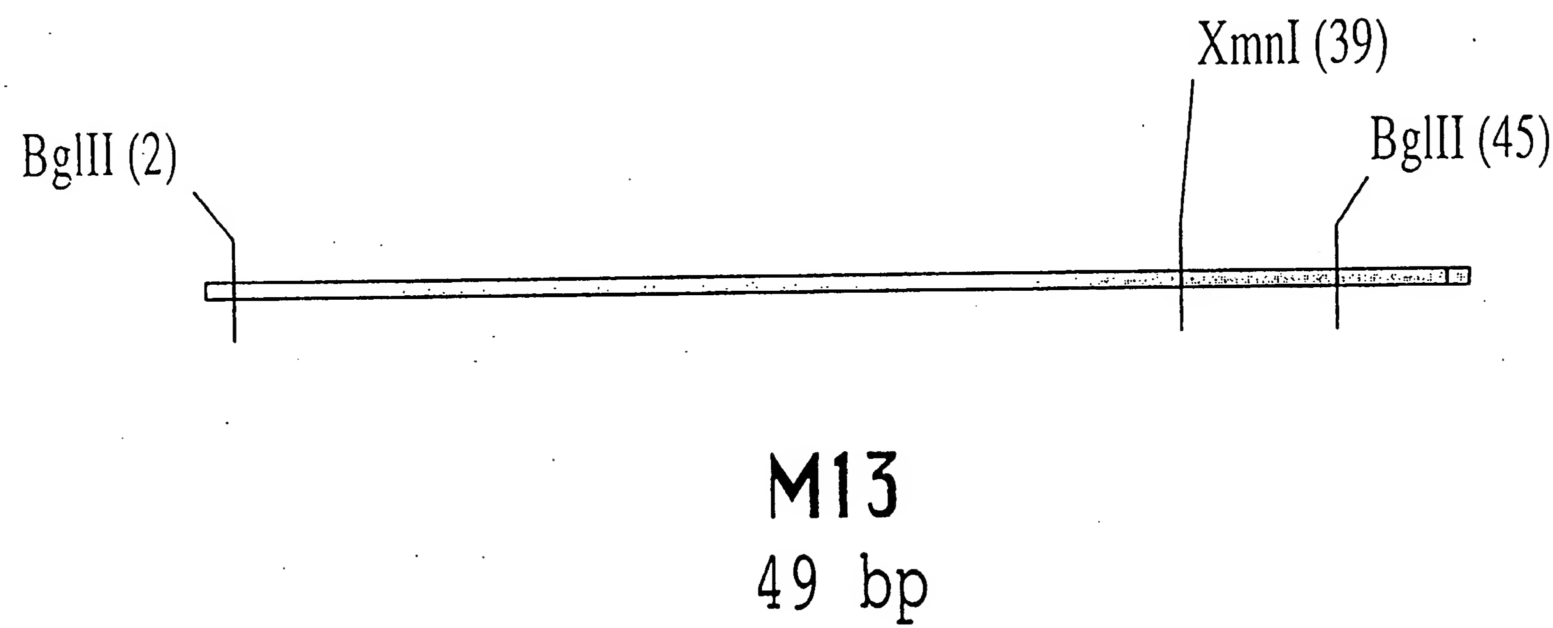


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 13:

```
     BglII                                            XmnI      BglII
     ~~~~~~~                                    ~~~~~~~~~~~~~~~~~~~
1    AGATCTCATA ACTTCGTATA ATGTATGCTA TACGAAGTTA TTCAGATCT
     TCTAGAGTAT TGAAGCATAT TACATACGAT ATGCTTCAAT AAGTCTAGA
```

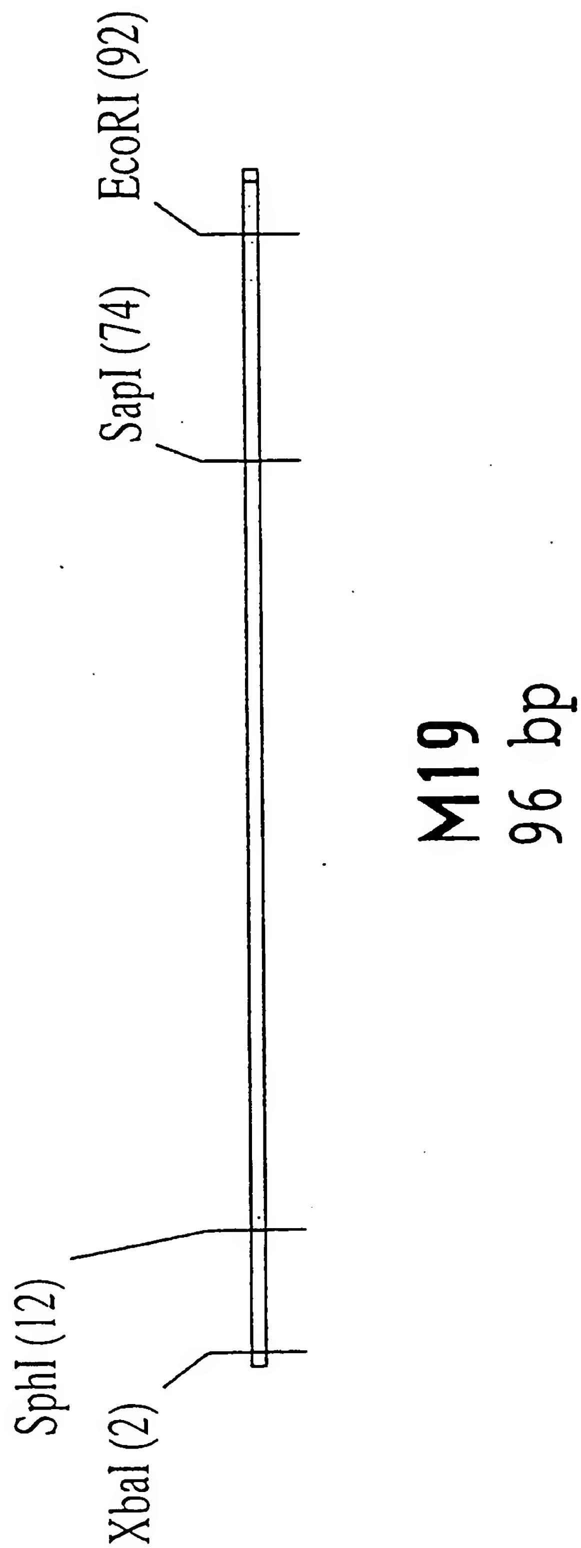


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 19:

```
      XbaI  SphI
     ~~~~~~~~~~~~~~~
 1   TCTAGAGCAT GCGTAGGAGA AAATAAAATG AAACAAAGCA CTATTGCACT
     AGATCTCGTA CGCATCCTCT TTTATTTTAC TTTGTTTCGT GATAACGTGA

                     SapI                        EcoRI
                  ~~~~~~~~~                      ~~~~~
51   GGCACTCTTA CCGTTGCTCT TCACCCCTGT TACCAAAGCC GAATTC
     CCGTGAGAAT GGCAACGAGA AGTGGGGACA ATGGTTTCGG CTTAAG
```

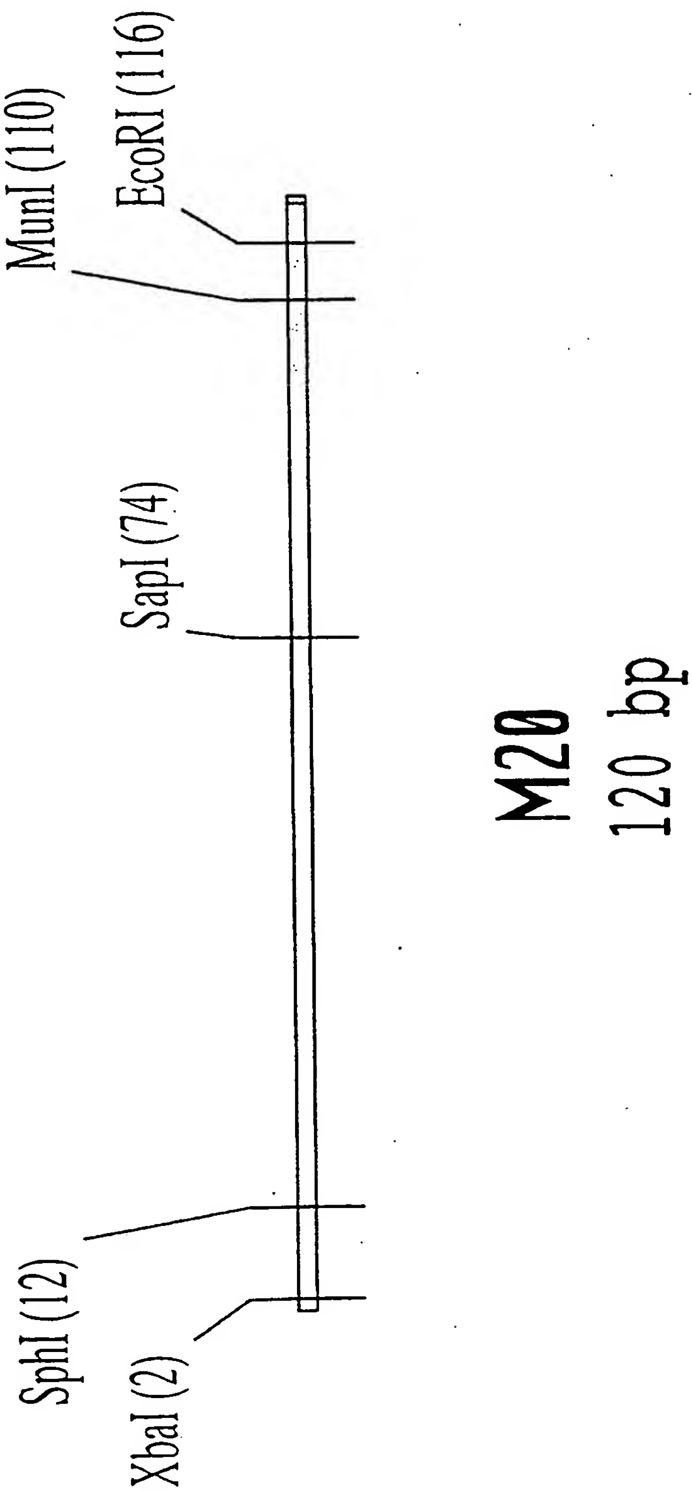


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
M 20:

        XbaI   SphI
       ~~~~~~~~~~~~~~
  1    TCTAGAGCAT GCGTAGGAGA AAATAAAATG AAACAAAGCA CTATTGCACT
       AGATCTCGTA CGCATCCTCT TTTATTTTAC TTTGTTTCGT GATAACGTGA

                         SapI
                       ~~~~~~~~~
 51    GGCACTCTTA CCGTTGCTCT TCACCCCTGT TACCAAAGCC GACTACAAAG
       CCGTGAGAAT GGCAACGAGA AGTGGGGACA ATGGTTTCGG CTGATGTTTC

                  MunI    EcoRI
                ~~~~~~~~~~~~~~
101    ATGAAGTGCA ATTGGAATTC
       TACTTCACGT TAACCTTAAG
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

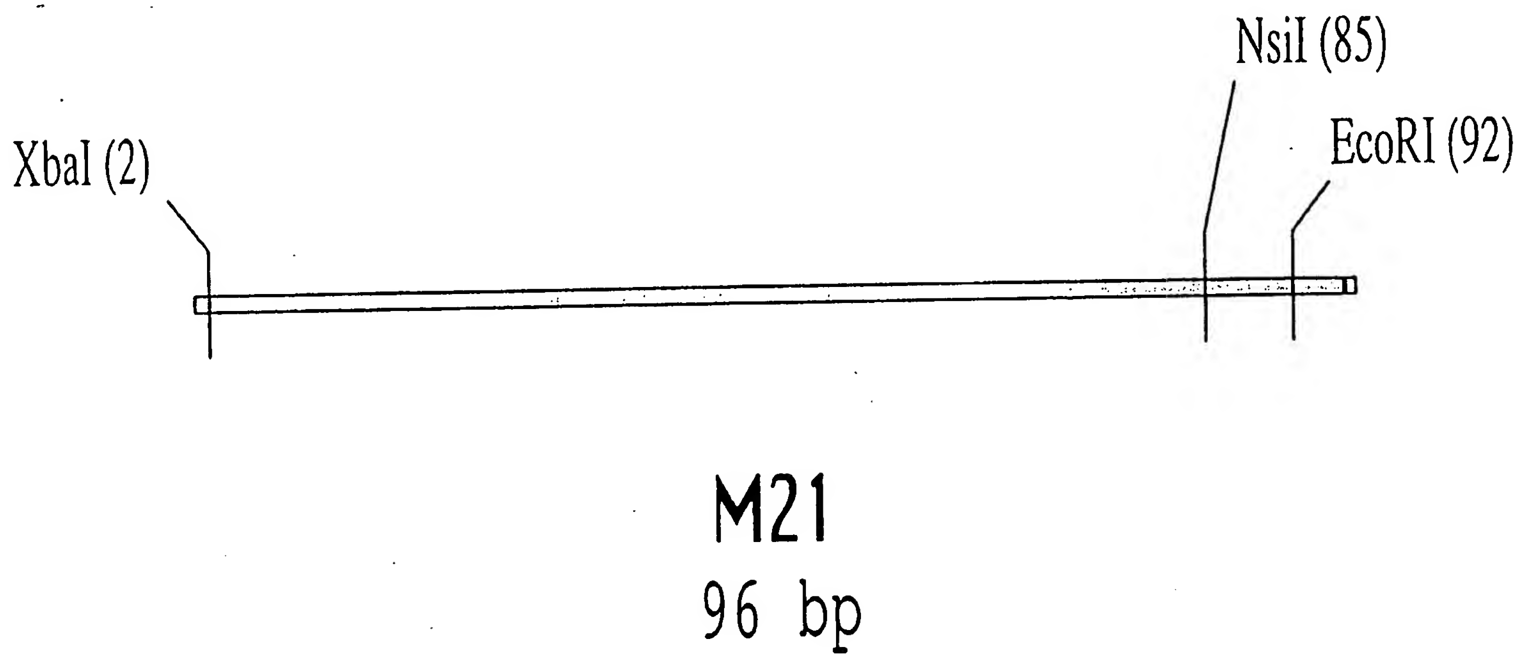


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 21:

```
      XbaI
    ~~~~~~~
 1  TCTAGAGGTT GAGGTGATTT TATGAAAAAG AATATCGCAT TTCTTCTTGC
    AGATCTCCAA CTCCACTAAA ATACTTTTTC TTATAGCGTA AAGAAGAACG

                                     NsiI        EcoRI
                                  ~~~~~~~~      ~~~~~~
51  ATCTATGTTC GTTTTTTCTA TTGCTACAAA TGCATACGCT GAATTC
    TAGATACAAG CAAAAAAGAT AACGATGTTT ACGTATGCGA CTTAAG
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

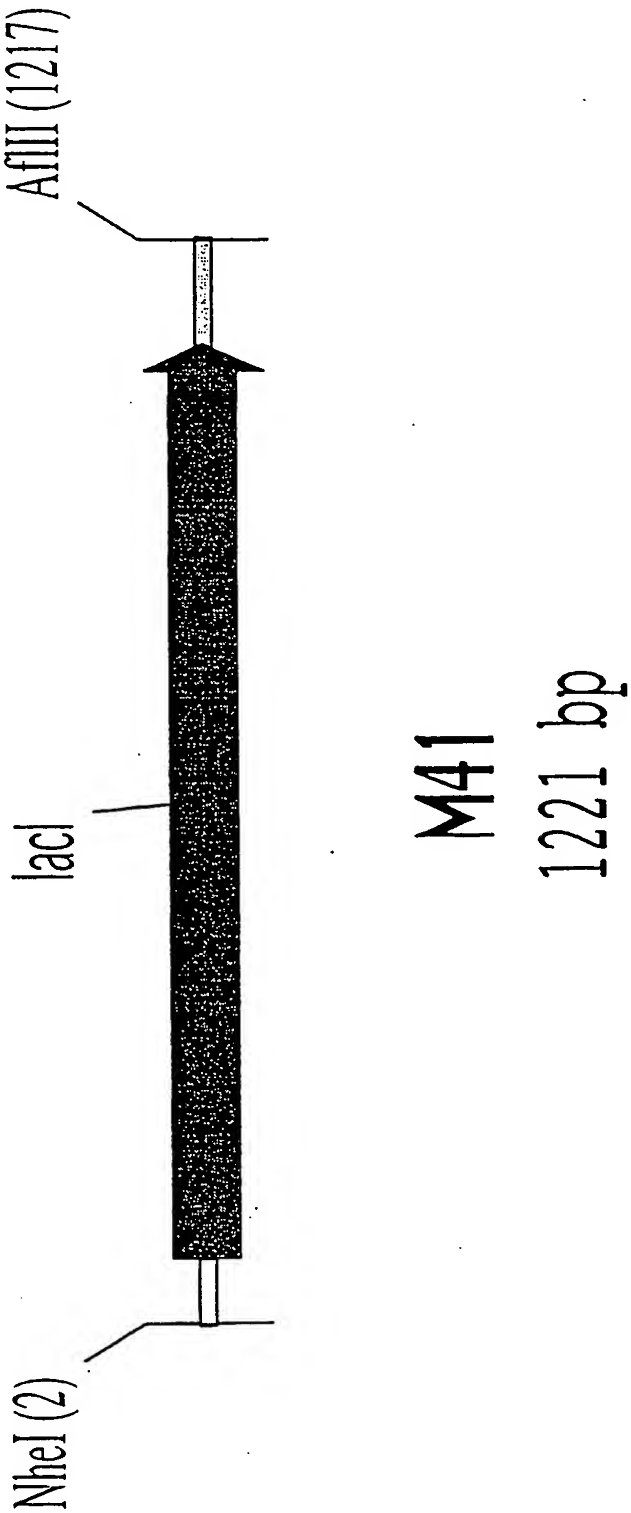


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 41:

```
          NheI
          ~~~~~~~
  1   GCTAGCATCG AATGGCGCAA AACCTTTCGC GGTATGGCAT GATAGCGCCC
      CGATCGTAGC TTACCGCGTT TTGGAAAGCG CCATACCGTA CTATCGCGGG

 51   GGAAGAGAGT CAATTCAGGG TGGTGAATGT GAAACCAGTA ACGTTATACG
      CCTTCTCTCA GTTAAGTCCC ACCACTTACA CTTTGGTCAT TGCAATATGC

101   ATGTCGCAGA GTATGCCGGT GTCTCTTATC AGACCGTTTC CCGCGTGGTG
      TACAGCGTCT CATACGGCCA CAGAGAATAG TCTGGCAAAG GGCGCACCAC

151   AACCAGGCCA GCCACGTTTC TGCGAAAACG CGGGAAAAAG TGGAAGCGGC
      TTGGTCCGGT CGGTGCAAAG ACGCTTTTGC GCCCTTTTTC ACCTTCGCCG

201   GATGGCGGAG CTGAATTACA TTCCTAACCG CGTGGCACAA CAACTGGCGG
      CTACCGCCTC GACTTAATGT AAGGATTGGC GCACCGTGTT GTTGACCGCC

251   GCAAACAGTC GTTGCTGATT GGCGTTGCCA CCTCCAGTCT GGCCCTGCAC
      CGTTTGTCAG CAACGACTAA CCGCAACGGT GGAGGTCAGA CCGGGACGTG

301   GCGCCGTCGC AAATTGTCGC GGCGATTAAA TCTCGCGCCG ATCAACTGGG
      CGCGGCAGCG TTTAACAGCG CCGCTAATTT AGAGCGCGGC TAGTTGACCC
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
351  TGCCAGCGTG GTCGTGTCGA TGGTAGAACG AAGCGGCGTC GAAGCCTGTA
     ACGGTCGCAC CAGCACAGCT ACCATCTTGC TTCGCCGCAG CTTCGGACAT

401  AAGCGGCGGT GCACAATCTT CTCGCGCAAC GTGTCAGTGG GCTGATTATT
     TTCGCCGCCA CGTGTTAGAA GAGCGCGTTG CACAGTCACC CGACTAATAA

451  AACTATCCGC TGGATGACCA GGATGCTATT GCTGTGGAAG CTGCCTGCAC
     TTGATAGGCG ACCTACTGGT CCTACGATAA CGACACCTTC GACGGACGTG

501  TAATGTTCCG GCGTTATTTC TTGATGTCTC TGACCAGACA CCCATCAACA
     ATTACAAGGC CGCAATAAAG AACTACAGAG ACTGGTCTGT GGGTAGTTGT

551  GTATTATTTT CTCCCATGAG GACGGTACGC GACTGGGCGT GGAGCATCTG
     CATAATAAAA GAGGGTACTC CTGCCATGCG CTGACCCGCA CCTCGTAGAC

601  GTCGCATTGG GCCACCAGCA AATCGCGCTG TTAGCTGGCC CATTAAGTTC
     CAGCGTAACC CGGTGGTCGT TTAGCGCGAC AATCGACCGG GTAATTCAAG

651  TGTCTCGGCG CGTCTGCGTC TGGCTGGCTG GCATAAATAT CTCACTCGCA
     ACAGAGCCGC GCAGACGCAG ACCGACCGAC CGTATTTATA GAGTGAGCGT

701  ATCAAATTCA GCCGATAGCG GAACGGGAAG GCGACTGGAG TGCCATGTCC
     TAGTTTAAGT CGGCTATCGC CTTGCCCTTC CGCTGACCTC ACGGTACAGG
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
751   GGTTTTCAAC AAACCATGCA AATGCTGAAT GAGGGCATCG TTCCCACTGC
      CCAAAAGTTG TTTGGTACGT TTACGACTTA CTCCCGTAGC AAGGGTGACG

801   GATGCTGGTT GCCAACGATC AGATGGCGCT GGGCGCAATG CGTGCCATTA
      CTACGACCAA CGGTTGCTAG TCTACCGCGA CCCGCGTTAC GCACGGTAAT

851   CCGAGTCCGG GCTGCGCGTT GGTGCGGACA TCTCGGTAGT GGGATACGAC
      GGCTCAGGCC CGACGCGCAA CCACGCCTGT AGAGCCATCA CCCTATGCTG

901   GATACCGAGG ACAGCTCATG TTATATCCCG CCGCTGACCA CCATCAAACA
      CTATGGCTCC TGTCGAGTAC AATATAGGGC GGCGACTGGT GGTAGTTTGT

951   GGATTTTCGC CTGCTGGGGC AAACCAGCGT GGACCGCTTG CTGCAACTCT
      CCTAAAAGCG GACGACCCCG TTTGGTCGCA CCTGGCGAAC GACGTTGAGA

1001  CTCAGGGCCA GGCGGTGAAG GGCAATCAGC TGTTGCCCGT CTCACTGGTG
      GAGTCCCGGT CCGCCACTTC CCGTTAGTCG ACAACGGGCA GAGTGACCAC

1051  AAAAGAAAAA CCACCCTGGC TCCCAATACG CAAACCGCCT CTCCCCGCGC
      TTTTCTTTTT GGTGGGACCG AGGGTTATGC GTTTGGCGGA GAGGGGCGCG

1101  GTTGGCCGAT TCACTGATGC AGCTGGCACG ACAGGTTTCC CGACTGGAAA
      CAACCGGCTA AGTGACTACG TCGACCGTGC TGTCCAAAGG GCTGACCTTT
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
1151  GCGGGCAGTG AGGCTACCCG ATAAAAGCGG CTTCCTGACA GGAGGCCGTT
      CGCCCGTCAC TCCGATGGGC TATTTTCGCC GAAGGACTGT CCTCCGGCAA

                          AflII
                         ~~~~~~~
1201  TTGTTTTGCA GCCCACTTAA G
      AACAAAACGT CGGGTGAATT C
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

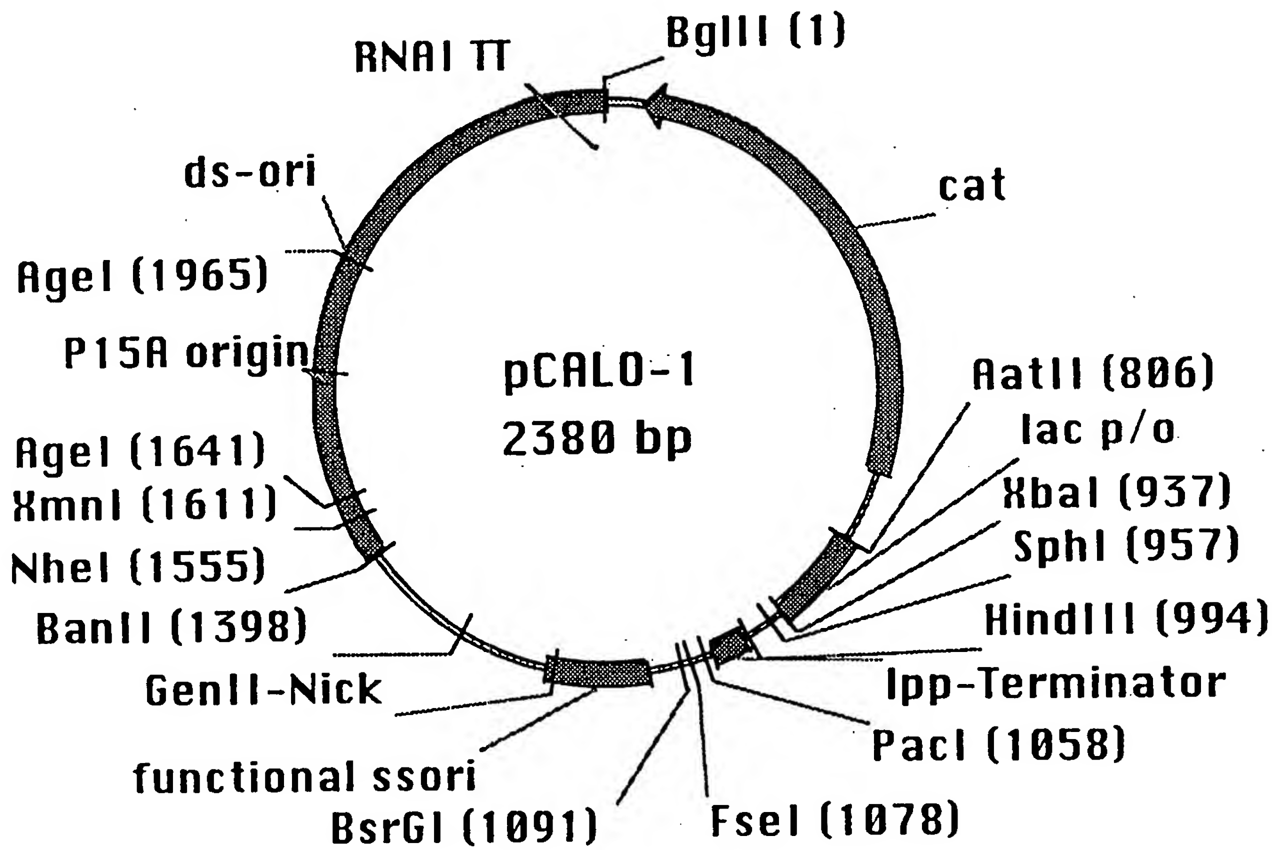


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

pCAL0-1:

```
       BglII
       ~~~~~~
  1    GATCTAGCAC CAGGCGTTTA AGGGCACCAA TAACTGCCTT AAAAAAATTA
       CTAGATCGTG GTCCGCAAAT TCCCGTGGTT ATTGACGGAA TTTTTTTAAT

 51    CGCCCCGCCC TGCCACTCAT CGCAGTACTG TTGTAATTCA TTAAGCATTC
       GCGGGGCGGG ACGGTGAGTA GCGTCATGAC AACATTAAGT AATTCGTAAG

101    TGCCGACATG GAAGCCATCA CAAACGGCAT GATGAACCTG AATCGCCAGC
       ACGGCTGTAC CTTCGGTAGT GTTTGCCGTA CTACTTGGAC TTAGCGGTCG

151    GGCATCAGCA CCTTGTCGCC TTGCGTATAA TATTTGCCCA TAGTGAAAAC
       CCGTAGTCGT GGAACAGCGG AACGCATATT ATAAACGGGT ATCACTTTTG

201    GGGGGCGAAG AAGTTGTCCA TATTGGCTAC GTTTAAATCA AAACTGGTGA
       CCCCCGCTTC TTCAACAGGT ATAACCGATG CAAATTTAGT TTTGACCACT

251    AACTCACCCA GGGATTGGCT GAGACGAAAA ACATATTCTC AATAAACCCT
       TTGAGTGGGT CCCTAACCGA CTCTGCTTTT TGTATAAGAG TTATTTGGGA

301    TTAGGGAAAT AGGCCAGGTT TTCACCGTAA CACGCCACAT CTTGCGAATA
       AATCCCTTTA TCCGGTCCAA AAGTGGCATT GTGCGGTGTA GAACGCTTAT
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
351  TATGTGTAGA AACTGCCGGA AATCGTCGTG GTATTCACTC CAGAGCGATG
     ATACACATCT TTGACGGCCT TTAGCAGCAC CATAAGTGAG GTCTCGCTAC

401  AAAACGTTTC AGTTTGCTCA TGGAAAACGG TGTAACAAGG GTGAACACTA
     TTTTGCAAAG TCAAACGAGT ACCTTTTGCC ACATTGTTCC CACTTGTGAT

451  TCCCATATCA CCAGCTCACC GTCTTTCATT GCCATACGGA ACTCCGGGTG
     AGGGTATAGT GGTCGAGTGG CAGAAAGTAA CGGTATGCCT TGAGGCCCAC

501  AGCATTCATC AGGCGGGCAA GAATGTGAAT AAAGGCCGGA TAAAACTTGT
     TCGTAAGTAG TCCGCCCGTT CTTACACTTA TTTCCGGCCT ATTTTGAACA

551  GCTTATTTTT CTTTACGGTC TTTAAAAAGG CCGTAATATC CAGCTGAACG
     CGAATAAAAA GAAATGCCAG AAATTTTTCC GGCATTATAG GTCGACTTGC

601  GTCTGGTTAT AGGTACATTG AGCAACTGAC TGAAATGCCT CAAAATGTTC
     CAGACCAATA TCCATGTAAC TCGTTGACTG ACTTTACGGA GTTTTACAAG

651  TTTACGATGC CATTGGGATA TATCAACGGT GGTATATCCA GTGATTTTTT
     AAATGCTACG GTAACCCTAT ATAGTTGCCA CCATATAGGT CACTAAAAAA

701  TCTCCATTTT AGCTTCCTTA GCTCCTGAAA ATCTCGATAA CTCAAAAAAT
     AGAGGTAAAA TCGAAGGAAT CGAGGACTTT TAGAGCTATT GAGTTTTTTA
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
751   ACGCCCGGTA GTGATCTTAT TTCATTATGG TGAAAGTTGG AACCTCACCC
      TGCGGGCCAT CACTAGAATA AAGTAATACC ACTTTCAACC TTGGAGTGGG

       AatII
      ~~~~~~~
801   GACGTCTAAT GTGAGTTAGC TCACTCATTA GGCACCCCAG GCTTTACACT
      CTGCAGATTA CACTCAATCG AGTGAGTAAT CCGTGGGGTC CGAAATGTGA

851   TTATGCTTCC GGCTCGTATG TTGTGTGGAA TTGTGAGCGG ATAACAATTT
      AATACGAAGG CCGAGCATAC AACACACCTT AACACTCGCC TATTGTTAAA

                                          XbaI
                                        ~~~~~~~~
901   CACACAGGAA ACAGCTATGA CCATGATTAC GAATTTCTAG ACCCCCCCCC
      GTGTGTCCTT TGTCGATACT GGTACTAATG CTTAAAGATC TGGGGGGGGG

        SphI                                       HindIII
      ~~~~~~~                                      ~~~~~~~
951   CGCATGCCAT AACTTCGTAT AATGTACGCT ATACGAAGTT ATAAGCTTGA
      GCGTACGGTA TTGAAGCATA TTACATGCGA TATGCTTCAA TATTCGAACT

1001  CCTGTGAAGT GAAAAATGGC GCAGATTGTG CGACATTTTT TTTGTCTGCC
      GGACACTTCA CTTTTTACCG CGTCTAACAC GCTGTAAAAA AAACAGACGG
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
                PacI                           FseI                           BsrGI
              ~~~~~~~~~                      ~~~~~~~~~                      ~~~~~~~~
1051   GTTTAATTAA  AGGGGGGGGG  GGGCCGGCCT  GGGGGGGGGT  GTACATGAAA
       CAAATTAATT  TCCCCCCCCC  CCCGGCCGGA  CCCCCCCCCA  CATGTACTTT

1101   TTGTAAACGT  TAATATTTTG  TTAAAATTCG  CGTTAAATTT  TTGTTAAATC
       AACATTTGCA  ATTATAAAAC  AATTTTAAGC  GCAATTTAAA  AACAATTTAG

1151   AGCTCATTTT  TTAACCAATA  GGCCGAAATC  GGCAAAATCC  CTTATAAATC
       TCGAGTAAAA  AATTGGTTAT  CCGGCTTTAG  CCGTTTTAGG  GAATATTTAG

1201   AAAAGAATAG  ACCGAGATAG  GGTTGAGTGT  TGTTCCAGTT  TGGAACAAGA
       TTTTCTTATC  TGGCTCTATC  CCAACTCACA  ACAAGGTCAA  ACCTTGTTCT

1251   GTCCACTATT  AAAGAACGTG  GACTCCAACG  TCAAAGGGCG  AAAAACCGTC
       CAGGTGATAA  TTTCTTGCAC  CTGAGGTTGC  AGTTTCCCGC  TTTTTGGCAG

1301   TATCAGGGCG  ATGGCCCACT  ACGAGAACCA  TCACCCTAAT  CAAGTTTTTT
       ATAGTCCCGC  TACCGGGTGA  TGCTCTTGGT  AGTGGGATTA  GTTCAAAAAA

                                                                BanII
                                                               ~~~~~~~
1351   GGGGTCGAGG  TGCCGTAAAG  CACTAAATCG  GAACCCTAAA  GGGAGCCCCC
       CCCCAGCTCC  ACGGCATTTC  GTGATTTAGC  CTTGGGATTT  CCCTCGGGGG
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
1401  GATTTAGAGC TTGACGGGGA AAGCCGGCGA ACGTGGCGAG AAAGGAAGGG
      CTAAATCTCG AACTGCCCCT TTCGGCCGCT TGCACCGCTC TTTCCTTCCC

1451  AAGAAAGCGA AAGGAGCGGG CGCTAGGGCG CTGGCAAGTG TAGCGGTCAC
      TTCTTTCGCT TTCCTCGCCC GCGATCCCGC GACCGTTCAC ATCGCCAGTG

1501  GCTGCGCGTA ACCACCACAC CCGCCGCGCT TAATGCGCCG CTACAGGGCG
      CGACGCGCAT TGGTGGTGTG GGCGGCGCGA ATTACGCGGC GATGTCCCGC

         NheI
       ~~~~~~~
1551  CGTGCTAGCG GAGTGTATAC TGGCTTACTA TGTTGGCACT GATGAGGGTG
      GCACGATCGC CTCACATATG ACCGAATGAT ACAACCGTGA CTACTCCCAC

             XmnI                                AgeI
        ~~~~~~~~~~~~                           ~~~~~~~~
1601  TCAGTGAAGT GCTTCATGTG GCAGGAGAAA AAAGGCTGCA CCGGTGCGTC
      AGTCACTTCA CGAAGTACAC CGTCCTCTTT TTTCCGACGT GGCCACGCAG

1651  AGCAGAATAT GTGATACAGG ATATATTCCG CTTCCTCGCT CACTGACTCG
      TCGTCTTATA CACTATGTCC TATATAAGGC GAAGGAGCGA GTGACTGAGC

1701  CTACGCTCGG TCGTTCGACT GCGGCGAGCG GAAATGGCTT ACGAACGGGG
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
                                                                  TGCTTGCCCC
        GATGCGAGCC  AGCAAGCTGA  CGCCGCTCGC  CTTTACCGAA

1751    CGGAGATTTC  CTGGAAGATG  CCAGGAAGAT  ACTTAACAGG  GAAGTGAGAG
        GCCTCTAAAG  GACCTTCTAC  GGTCCTTCTA  TGAATTGTCC  CTTCACTCTC

1801    GGCCGCGGCA  AAGCCGTTTT  TCCATAGGCT  CCGCCCCCCT  GACAAGCATC
        CCGGCGCCGT  TTCGGCAAAA  AGGTATCCGA  GGCGGGGGGA  CTGTTCGTAG

1851    ACGAAATCTG  ACGCTCAAAT  CAGTGGTGGC  GAAACCCGAC  AGGACTATAA
        TGCTTTAGAC  TGCGAGTTTA  GTCACCACCG  CTTTGGGCTG  TCCTGATATT

1901    AGATACCAGG  CGTTTCCCCC  TGGCGGCTCC  CTCCTGCGCT  CTCCTGTTCC
        TCTATGGTCC  GCAAAGGGGG  ACCGCCGAGG  GAGGACGCGA  GAGGACAAGG

                       AgeI
                     ~~~~~~
1951    TGCCTTTCGG  TTTACCGGTG  TCATTCCGCT  GTTATGGCCG  CGTTTGTCTC
        ACGGAAAGCC  AAATGGCCAC  AGTAAGGCGA  CAATACCGGC  GCAAACAGAG

2001    ATTCCACGCC  TGACACTCAG  TTCCGGGTAG  GCAGTTCGCT  CCAAGCTGGA
        TAAGGTGCGG  ACTGTGAGTC  AAGGCCCATC  CGTCAAGCGA  GGTTCGACCT

2051    CTGTATGCAC  GAACCCCCCG  TTCAGTCCGA  CCGCTGCGCC  TTATCCGGTA
        GACATACGTG  CTTGGGGGGC  AAGTCAGGCT  GGCGACGCGG  AATAGGCCAT
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
2101   ACTATCGTCT TGAGTCCAAC CCGGAAAGAC ATGCAAAAGC ACCACTGGCA
       TGATAGCAGA ACTCAGGTTG GGCCTTTCTG TACGTTTTCG TGGTGACCGT

2151   GCAGCCACTG GTAATTGATT TAGAGGAGTT AGTCTTGAAG TCATGCGCCG
       CGTCGGTGAC CATTAACTAA ATCTCCTCAA TCAGAACTTC AGTACGCGGC

2201   GTTAAGGCTA AACTGAAAGG ACAAGTTTTA GTGACTGCGC TCCTCCAAGC
       CAATTCCGAT TTGACTTTCC TGTTCAAAAT CACTGACGCG AGGAGGTTCG

2251   CAGTTACCTC GGTTCAAAGA GTTGGTAGCT CAGAGAACCT ACGAAAAACC
       GTCAATGGAG CCAAGTTTCT CAACCATCGA GTCTCTTGGA TGCTTTTTGG

2301   GCCCTGCAAG GCGGTTTTTT CGTTTTCAGA GCAAGAGATT ACGCGCAGAC
       CGGGACGTTC CGCCAAAAAA GCAAAAGTCT CGTTCTCTAA TGCGCGTCTG

                                  BglII
                                      ~
2351   CAAAACGATC TCAAGAAGAT CATCTTATTA
       GTTTTGCTAG AGTTCTTCTA GTAGAATAAT
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

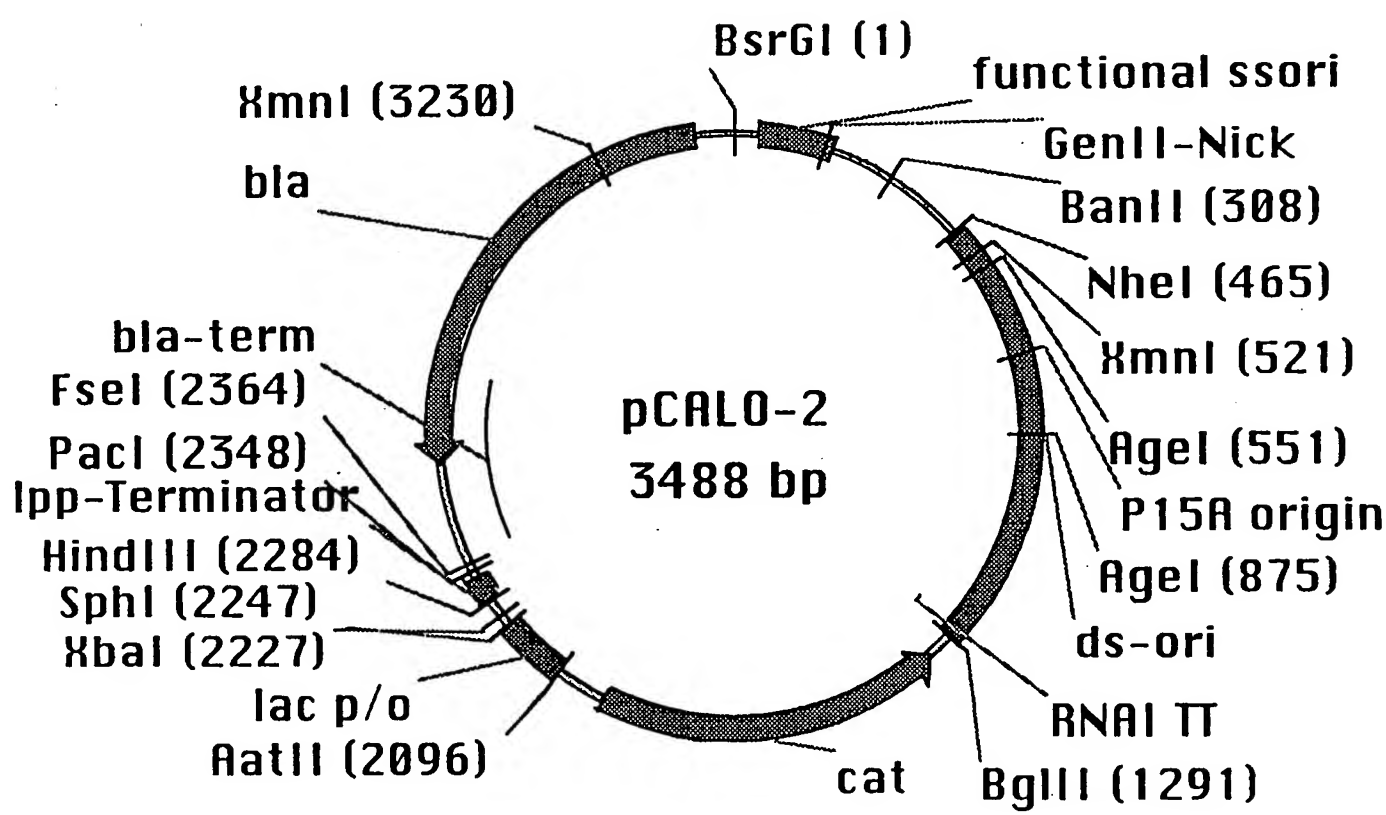


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

pCALO-2:

```
       BsrGI
       ~~~~~
  1    GTACATGAAA TTGTAAACGT TAATATTTTG TTAAAATTCG CGTTAAATTT
       CATGTACTTT AACATTTGCA ATTATAAAAC AATTTTAAGC GCAATTTAAA

 51    TTGTTAAATC AGCTCATTTT TTAACCAATA GGCCGAAATC GGCAAAATCC
       AACAATTTAG TCGAGTAAAA AATTGGTTAT CCGGCTTTAG CCGTTTTAGG

101    CTTATAAATC AAAAGAATAG ACCGAGATAG GGTTGAGTGT TGTTCCAGTT
       GAATATTTAG TTTTCTTATC TGGCTCTATC CCAACTCACA ACAAGGTCAA

151    TGGAACAAGA GTCCACTATT AAAGAACGTG GACTCCAACG TCAAAGGGCG
       ACCTTGTTCT CAGGTGATAA TTTCTTGCAC CTGAGGTTGC AGTTTCCCGC

201    AAAAACCGTC TATCAGGGCG ATGGCCCACT ACGAGAACCA TCACCCTAAT
       TTTTTGGCAG ATAGTCCCGC TACCGGGTGA TGCTCTTGGT AGTGGGATTA

251    CAAGTTTTTT GGGGTCGAGG TGCCGTAAAG CACTAAATCG GAACCCTAAA
       GTTCAAAAAA CCCCAGCTCC ACGGCATTTC GTGATTTAGC CTTGGGATTT

          BanII
         ~~~~~~~
301    GGGAGCCCCC GATTTAGAGC TTGACGGGGA AAGCCGGCGA ACGTGGCGAG
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
        CCCTCGGGGG CTAAATCTCG AACTGCCCCT TTCGGCCGCT TGCACCGCTC

351     AAAGGAAGGG AAGAAAGCGA AAGGAGCGGG CGCTAGGGCG CTGGCAAGTG
        TTTCCTTCCC TTCTTTCGCT TTCCTCGCCC GCGATCCCGC GACCGTTCAC

401     TAGCGGTCAC GCTGCGCGTA ACCACCACAC CCGCCGCGCT TAATGCGCCG
        ATCGCCAGTG CGACGCGCAT TGGTGGTGTG GGCGGCGCGA ATTACGCGGC

                      NheI
                     ~~~~~~~
451     CTACAGGGCG CGTGCTAGCG GAGTGTATAC TGGCTTACTA TGTTGGCACT
        GATGTCCCGC GCACGATCGC CTCACATATG ACCGAATGAT ACAACCGTGA

                          XmnI                            AgeI
                      ~~~~~~~~~~~~                           ~
501     GATGAGGGTG TCAGTGAAGT GCTTCATGTG GCAGGAGAAA AAAGGCTGCA
        CTACTCCCAC AGTCACTTCA CGAAGTACAC CGTCCTCTTT TTTCCGACGT

        AgeI
        ~~~~~
551     CCGGTGCGTC AGCAGAATAT GTGATACAGG ATATATTCCG CTTCCTCGCT
        GGCCACGCAG TCGTCTTATA CACTATGTCC TATATAAGGC GAAGGAGCGA

601     CACTGACTCG CTACGCTCGG TCGTTCGACT GCGGCGAGCG GAAATGGCTT
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
       GTGACTGAGC GATGCGAGCC AGCAAGCTGA CGCCGCTCGC CTTTACCGAA

651    ACGAACGGGG CGGAGATTTC CTGGAAGATG CCAGGAAGAT ACTTAACAGG
       TGCTTGCCCC GCCTCTAAAG GACCTTCTAC GGTCCTTCTA TGAATTGTCC

701    GAAGTGAGAG GGCCGCGGCA AAGCCGTTTT TCCATAGGCT CCGCCCCCCT
       CTTCACTCTC CCGGCGCCGT TTCGGCAAAA AGGTATCCGA GGCGGGGGGA

751    GACAAGCATC ACGAAATCTG ACGCTCAAAT CAGTGGTGGC GAAACCCGAC
       CTGTTCGTAG TGCTTTAGAC TGCGAGTTTA GTCACCACCG CTTTGGGCTG

801    AGGACTATAA AGATACCAGG CGTTTCCCCC TGGCGGCTCC CTCCTGCGCT
       TCCTGATATT TCTATGGTCC GCAAAGGGGG ACCGCCGAGG GAGGACGCGA

                                AgeI
                               ~~~~~~
851    CTCCTGTTCC TGCCTTTCGG TTTACCGGTG TCATTCCGCT GTTATGGCCG
       GAGGACAAGG ACGGAAAGCC AAATGGCCAC AGTAAGGCGA CAATACCGGC

901    CGTTTGTCTC ATTCCACGCC TGACACTCAG TTCCGGGTAG GCAGTTCGCT
       GCAAACAGAG TAAGGTGCGG ACTGTGAGTC AAGGCCCATC CGTCAAGCGA

951    CCAAGCTGGA CTGTATGCAC GAACCCCCCG TTCAGTCCGA CCGCTGCGCC
       GGTTCGACCT GACATACGTG CTTGGGGGGC AAGTCAGGCT GGCGACGCGG
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
1001   TTATCCGGTA ACTATCGTCT TGAGTCCAAC CCGGAAAGAC ATGCAAAAGC
       AATAGGCCAT TGATAGCAGA ACTCAGGTTG GGCCTTTCTG TACGTTTTCG

1051   ACCACTGGCA GCAGCCACTG GTAATTGATT TAGAGGAGTT AGTCTTGAAG
       TGGTGACCGT CGTCGGTGAC CATTAACTAA ATCTCCTCAA TCAGAACTTC

1101   TCATGCGCCG GTTAAGGCTA AACTGAAAGG ACAAGTTTTA GTGACTGCGC
       AGTACGCGGC CAATTCCGAT TTGACTTTCC TGTTCAAAAT CACTGACGCG

1151   TCCTCCAAGC CAGTTACCTC GGTTCAAAGA GTTGGTAGCT CAGAGAACCT
       AGGAGGTTCG GTCAATGGAG CCAAGTTTCT CAACCATCGA GTCTCTTGGA

1201   ACGAAAAACC GCCCTGCAAG GCGGTTTTTT CGTTTTCAGA GCAAGAGATT
       TGCTTTTTGG CGGGACGTTC CGCCAAAAAA GCAAAAGTCT CGTTCTCTAA

                                                  BglII
                                                ~~~~~~~~
1251   ACGCGCAGAC CAAAACGATC TCAAGAAGAT CATCTTATTA GATCTAGCAC
       TGCGCGTCTG GTTTTGCTAG AGTTCTTCTA GTAGAATAAT CTAGATCGTG

1301   CAGGCGTTTA AGGGCACCAA TAACTGCCTT AAAAAAATTA CGCCCCGCCC
       GTCCGCAAAT TCCCGTGGTT ATTGACGGAA TTTTTTTAAT GCGGGGCGGG
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
1351  TGCCACTCAT CGCAGTACTG TTGTAATTCA TTAAGCATTC TGCCGACATG
      ACGGTGAGTA GCGTCATGAC AACATTAAGT AATTCGTAAG ACGGCTGTAC

1401  GAAGCCATCA CAAACGGCAT GATGAACCTG AATCGCCAGC GGCATCAGCA
      CTTCGGTAGT GTTTGCCGTA CTACTTGGAC TTAGCGGTCG CCGTAGTCGT

1451  CCTTGTCGCC TTGCGTATAA TATTTGCCCA TAGTGAAAAC GGGGGCGAAG
      GGAACAGCGG AACGCATATT ATAAACGGGT ATCACTTTTG CCCCCGCTTC

1501  AAGTTGTCCA TATTGGCTAC GTTTAAATCA AAACTGGTGA AACTCACCCA
      TTCAACAGGT ATAACCGATG CAAATTTAGT TTTGACCACT TTGAGTGGGT

1551  GGGATTGGCT GAGACGAAAA ACATATTCTC AATAAACCCT TTAGGGAAAT
      CCCTAACCGA CTCTGCTTTT TGTATAAGAG TTATTTGGGA AATCCCTTTA

1601  AGGCCAGGTT TTCACCGTAA CACGCCACAT CTTGCGAATA TATGTGTAGA
      TCCGGTCCAA AAGTGGCATT GTGCGGTGTA GAACGCTTAT ATACACATCT

1651  AACTGCCGGA AATCGTCGTG GTATTCACTC CAGAGCGATG AAAACGTTTC
      TTGACGGCCT TTAGCAGCAC CATAAGTGAG GTCTCGCTAC TTTTGCAAAG

1701  AGTTTGCTCA TGGAAAACGG TGTAACAAGG GTGAACACTA TCCCATATCA
      TCAAACGAGT ACCTTTTGCC ACATTGTTCC CACTTGTGAT AGGGTATAGT
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
1751  CCAGCTCACC GTCTTTCATT GCCATACGGA ACTCCGGGTG AGCATTCATC
      GGTCGAGTGG CAGAAAGTAA CGGTATGCCT TGAGGCCCAC TCGTAAGTAG

1801  AGGCGGGCAA GAATGTGAAT AAAGGCCGGA TAAAACTTGT GCTTATTTTT
      TCCGCCCGTT CTTACACTTA TTTCCGGCCT ATTTTGAACA CGAATAAAAA

1851  CTTTACGGTC TTTAAAAAGG CCGTAATATC CAGCTGAACG GTCTGGTTAT
      GAAATGCCAG AAATTTTTCC GGCATTATAG GTCGACTTGC CAGACCAATA

1901  AGGTACATTG AGCAACTGAC TGAAATGCCT CAAAATGTTC TTTACGATGC
      TCCATGTAAC TCGTTGACTG ACTTTACGGA GTTTTACAAG AAATGCTACG

1951  CATTGGGATA TATCAACGGT GGTATATCCA GTGATTTTTT TCTCCATTTT
      GTAACCCTAT ATAGTTGCCA CCATATAGGT CACTAAAAAA AGAGGTAAAA

2001  AGCTTCCTTA GCTCCTGAAA ATCTCGATAA CTCAAAAAAT ACGCCCGGTA
      TCGAAGGAAT CGAGGACTTT TAGAGCTATT GAGTTTTTTA TGCGGGCCAT

                                               AatII
                                               ~~~~~~
2051  GTGATCTTAT TTCATTATGG TGAAAGTTGG AACCTCACCC GACGTCTAAT
      CACTAGAATA AAGTAATACC ACTTTCAACC TTGGAGTGGG CTGCAGATTA

2101  GTGAGTTAGC TCACTCATTA GGCACCCCAG GCTTTACACT TTATGCTTCC
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
      CACTCAATCG AGTGAGTAAT CCGTGGGGTC CGAAATGTGA AATACGAAGG

2151  GGCTCGTATG TTGTGTGGAA TTGTGAGCGG ATAACAATTT CACACAGGAA
      CCGAGCATAC AACACACCTT AACACTCGCC TATTGTTAAA GTGTGTCCTT

                                 XbaI                  SphI
                               ~~~~~~~~              ~~~~~~
2201  ACAGCTATGA CCATGATTAC GAATTTCTAG ACCCCCCCCC CGCATGCCAT
      TGTCGATACT GGTACTAATG CTTAAAGATC TGGGGGGGGG GCGTACGGTA

                                       HindIII
                                       ~~~~~~
2251  AACTTCGTAT AATGTACGCT ATACGAAGTT ATAAGCTTGA CCTGTGAAGT
      TTGAAGCATA TTACATGCGA TATGCTTCAA TATTCGAACT GGACACTTCA

                                                     PacI
                                                  ~~~~~~~~~
2301  GAAAAATGGC GCAGATTGTG CGACATTTTT TTTGTCTGCC GTTTAATTAA
      CTTTTTACCG CGTCTAACAC GCTGTAAAAA AAACAGACGG CAAATTAATT

                FseI
            ~~~~~~~~~~
2351  GGGGGGGGGC CGGCCATTAT CAAAAAGGAT CTCAAGAAGA TCCTTTGATC
      CCCCCCCCCG GCCGGTAATA GTTTTTCCTA GAGTTCTTCT AGGAAACTAG
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
2401  TTTTCTACGG GGTCTGACGC TCAGTGGAAC GAAAACTCAC GTTAAGGGAT
      AAAAGATGCC CCAGACTGCG AGTCACCTTG CTTTTGAGTG CAATTCCCTA

2451  TTTGGTCATG AGATTATCAA AAAGGATCTT CACCTAGATC CTTTTAAATT
      AAACCAGTAC TCTAATAGTT TTTCCTAGAA GTGGATCTAG GAAAATTTAA

2501  AAAAATGAAG TTTTAAATCA ATCTAAAGTA TATATGAGTA AACTTGGTCT
      TTTTTACTTC AAAATTTAGT TAGATTTCAT ATATACTCAT TTGAACCAGA

2551  GACAGTTACC CAATGCTTAA TCAGTGAGGC ACCTATCTCA GCGATCTGTC
      CTGTCAATGG GTTACGAATT AGTCACTCCG TGGATAGAGT CGCTAGACAG

2601  TATTTCGTTC ATCCATAGTT GCCTGACTCC CCGTCGTGTA GATAACTACG
      ATAAAGCAAG TAGGTATCAA CGGACTGAGG GGCAGCACAT CTATTGATGC

2651  ATACGGGAGG GCTTACCATC TGGCCCCAGT GCTGCAATGA TACCGCGAGA
      TATGCCCTCC CGAATGGTAG ACCGGGGTCA CGACGTTACT ATGGCGCTCT

2701  CCCACGCTCA CCGGCTCCAG ATTTATCAGC AATAAACCAG CCAGCCGGAA
      GGGTGCGAGT GGCCGAGGTC TAAATAGTCG TTATTTGGTC GGTCGGCCTT

2751  GGGCCGAGCG CAGAAGTGGT CCTGCAACTT TATCCGCCTC CATCCAGTCT
      CCCGGCTCGC GTCTTCACCA GGACGTTGAA ATAGGCGGAG GTAGGTCAGA
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
2801  ATTAACTGTT GCCGGGAAGC TAGAGTAAGT AGTTCGCCAG TTAATAGTTT
      TAATTGACAA CGGCCCTTCG ATCTCATTCA TCAAGCGGTC AATTATCAAA

2851  GCGCAACGTT GTTGCCATTG CTACAGGCAT CGTGGTGTCA CGCTCGTCGT
      CGCGTTGCAA CAACGGTAAC GATGTCCGTA GCACCACAGT GCGAGCAGCA

2901  TTGGTATGGC TTCATTCAGC TCCGGTTCCC AACGATCAAG GCGAGTTACA
      AACCATACCG AAGTAAGTCG AGGCCAAGGG TTGCTAGTTC CGCTCAATGT

2951  TGATCCCCCA TGTTGTGCAA AAAAGCGGTT AGCTCCTTCG GTCCTCCGAT
      ACTAGGGGGT ACAACACGTT TTTTCGCCAA TCGAGGAAGC CAGGAGGCTA

3001  CGTTGTCAGA AGTAAGTTGG CCGCAGTGTT ATCACTCATG GTTATGGCAG
      GCAACAGTCT TCATTCAACC GGCGTCACAA TAGTGAGTAC CAATACCGTC

3051  CACTGCATAA TTCTCTTACT GTCATGCCAT CCGTAAGATG CTTTTCTGTG
      GTGACGTATT AAGAGAATGA CAGTACGGTA GGCATTCTAC GAAAAGACAC

3101  ACTGGTGAGT ACTCAACCAA GTCATTCTGA GAATAGTGTA TGCGGCGACC
      TGACCACTCA TGAGTTGGTT CAGTAAGACT CTTATCACAT ACGCCGCTGG

3151  GAGTTGCTCT TGCCCGGCGT CAATACGGGA TAATACCGCG CCACATAGCA
      CTCAACGAGA ACGGGCCGCA GTTATGCCCT ATTATGGCGC GGTGTATCGT
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
                                            XmnI
                                          ~~~~~~~~~~~~~
3201  GAACTTTAAA AGTGCTCATC ATTGGAAAAC GTTCTTCGGG GCGAAAACTC
      CTTGAAATTT TCACGAGTAG TAACCTTTTG CAAGAAGCCC CGCTTTTGAG

3251  TCAAGGATCT TACCGCTGTT GAGATCCAGT TCGATGTAAC CCACTCGCGC
      AGTTCCTAGA ATGGCGACAA CTCTAGGTCA AGCTACATTG GGTGAGCGCG

3301  ACCCAACTGA TCCTCAGCAT CTTTTACTTT CACCAGCGTT TCTGGGTGAG
      TGGGTTGACT AGGAGTCGTA GAAAATGAAA GTGGTCGCAA AGACCCACTC

3351  CAAAAACAGG AAGGCAAAAT GCCGCAAAAA AGGGAATAAG GGCGACACGG
      GTTTTTGTCC TTCCGTTTTA CGGCGTTTTT TCCCTTATTC CCGCTGTGCC

3401  AAATGTTGAA TACTCATACT CTTCCTTTTT CAATATTATT GAAGCATTTA
      TTTACAACTT ATGAGTATGA GAAGGAAAAA GTTATAATAA CTTCGTAAAT

                                         BsrGI

3451  TCAGGGTTAT TGTCTCATGA GCGGATACAT ATTTGAAT
      AGTCCCAATA ACAGAGTACT CGCCTATGTA TAAACTTA
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

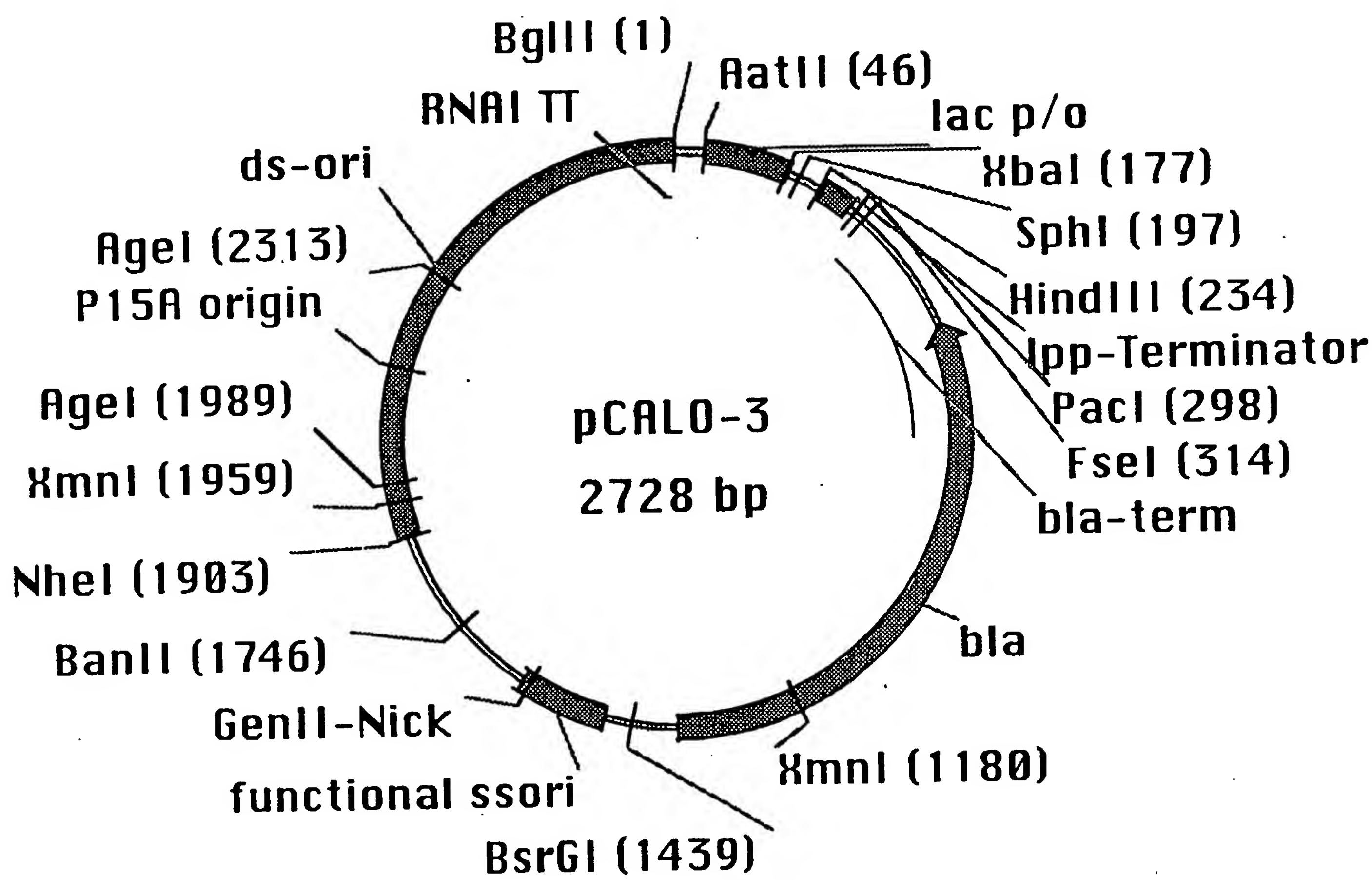


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

pCALO-3:

```
        BglII                                                  AatII
        ~~~~~~                                                 ~~~~~~~
  1     GATCTCATAA CTTCGTATAA TGTATGCTAT ACGAAGTTAT GACGTCTAAT
        CTAGAGTATT GAAGCATATT ACATACGATA TGCTTCAATA CTGCAGATTA

 51     GTGAGTTAGC TCACTCATTA GGCACCCCAG GCTTTACACT TTATGCTTCC
        CACTCAATCG AGTGAGTAAT CCGTGGGGTC CGAAATGTGA AATACGAAGG

101     GGCTCGTATG TTGTGTGGAA TTGTGAGCGG ATAACAATTT CACACAGGAA
        CCGAGCATAC AACACACCTT AACACTCGCC TATTGTTAAA GTGTGTCCTT

                                  XbaI                 SphI
                               ~~~~~~~~             ~~~~~~~
151     ACAGCTATGA CCATGATTAC GAATTTCTAG ACCCCCCCCC CGCATGCCAT
        TGTCGATACT GGTACTAATG CTTAAAGATC TGGGGGGGGG GCGTACGGTA

                                            HindIII
                                            ~~~~~~~
201     AACTTCGTAT AATGTACGCT ATACGAAGTT ATAAGCTTGA CCTGTGAAGT
        TTGAAGCATA TTACATGCGA TATGCTTCAA TATTCGAACT GGACACTTCA

                                                        PacI
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
                                                      ~~~~~~~~~
251  GAAAAATGGC GCAGATTGTG CGACATTTTT TTTGTCTGCC GTTTAATTAA
     CTTTTTACCG CGTCTAACAC GCTGTAAAAA AAACAGACGG CAAATTAATT

           FseI
         ~~~~~~~~~~
301  GGGGGGGGGC CGGCCATTAT CAAAAAGGAT CTCAAGAAGA TCCTTTGATC
     CCCCCCCCCG GCCGGTAATA GTTTTTCCTA GAGTTCTTCT AGGAAACTAG

351  TTTTCTACGG GGTCTGACGC TCAGTGGAAC GAAAACTCAC GTTAAGGGAT
     AAAAGATGCC CCAGACTGCG AGTCACCTTG CTTTTGAGTG CAATTCCCTA

401  TTTGGTCATG AGATTATCAA AAAGGATCTT CACCTAGATC CTTTTAAATT
     AAACCAGTAC TCTAATAGTT TTTCCTAGAA GTGGATCTAG GAAAATTTAA

451  AAAAATGAAG TTTTAAATCA ATCTAAAGTA TATATGAGTA AACTTGGTCT
     TTTTTACTTC AAAATTTAGT TAGATTTCAT ATATACTCAT TTGAACCAGA

501  GACAGTTACC CAATGCTTAA TCAGTGAGGC ACCTATCTCA GCGATCTGTC
     CTGTCAATGG GTTACGAATT AGTCACTCCG TGGATAGAGT CGCTAGACAG

551  TATTTCGTTC ATCCATAGTT GCCTGACTCC CCGTCGTGTA GATAACTACG
     ATAAAGCAAG TAGGTATCAA CGGACTGAGG GGCAGCACAT CTATTGATGC
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
601  ATACGGGAGG GCTTACCATC TGGCCCCAGT GCTGCAATGA TACCGCGAGA
     TATGCCCTCC CGAATGGTAG ACCGGGGTCA CGACGTTACT ATGGCGCTCT

651  CCCACGCTCA CCGGCTCCAG ATTTATCAGC AATAAACCAG CCAGCCGGAA
     GGGTGCGAGT GGCCGAGGTC TAAATAGTCG TTATTTGGTC GGTCGGCCTT

701  GGGCCGAGCG CAGAAGTGGT CCTGCAACTT TATCCGCCTC CATCCAGTCT
     CCCGGCTCGC GTCTTCACCA GGACGTTGAA ATAGGCGGAG GTAGGTCAGA

751  ATTAACTGTT GCCGGGAAGC TAGAGTAAGT AGTTCGCCAG TTAATAGTTT
     TAATTGACAA CGGCCCTTCG ATCTCATTCA TCAAGCGGTC AATTATCAAA

801  GCGCAACGTT GTTGCCATTG CTACAGGCAT CGTGGTGTCA CGCTCGTCGT
     CGCGTTGCAA CAACGGTAAC GATGTCCGTA GCACCACAGT GCGAGCAGCA

851  TTGGTATGGC TTCATTCAGC TCCGGTTCCC AACGATCAAG GCGAGTTACA
     AACCATACCG AAGTAAGTCG AGGCCAAGGG TTGCTAGTTC CGCTCAATGT

901  TGATCCCCCA TGTTGTGCAA AAAAGCGGTT AGCTCCTTCG GTCCTCCGAT
     ACTAGGGGGT ACAACACGTT TTTTCGCCAA TCGAGGAAGC CAGGAGGCTA

951  CGTTGTCAGA AGTAAGTTGG CCGCAGTGTT ATCACTCATG GTTATGGCAG
     GCAACAGTCT TCATTCAACC GGCGTCACAA TAGTGAGTAC CAATACCGTC
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
1001   CACTGCATAA TTCTCTTACT GTCATGCCAT CCGTAAGATG CTTTTCTGTG
       GTGACGTATT AAGAGAATGA CAGTACGGTA GGCATTCTAC GAAAAGACAC

1051   ACTGGTGAGT ACTCAACCAA GTCATTCTGA GAATAGTGTA TGCGGCGACC
       TGACCACTCA TGAGTTGGTT CAGTAAGACT CTTATCACAT ACGCCGCTGG

1101   GAGTTGCTCT TGCCCGGCGT CAATACGGGA TAATACCGCG CCACATAGCA
       CTCAACGAGA ACGGGCCGCA GTTATGCCCT ATTATGGCGC GGTGTATCGT

                                   XmnI
                              ~~~~~~~~~~~~~
1151   GAACTTTAAA AGTGCTCATC ATTGGAAAAC GTTCTTCGGG GCGAAAACTC
       CTTGAAATTT TCACGAGTAG TAACCTTTTG CAAGAAGCCC CGCTTTTGAG

1201   TCAAGGATCT TACCGCTGTT GAGATCCAGT TCGATGTAAC CCACTCGCGC
       AGTTCCTAGA ATGGCGACAA CTCTAGGTCA AGCTACATTG GGTGAGCGCG

1251   ACCCAACTGA TCCTCAGCAT CTTTTACTTT CACCAGCGTT TCTGGGTGAG
       TGGGTTGACT AGGAGTCGTA GAAAATGAAA GTGGTCGCAA AGACCCACTC

1301   CAAAAACAGG AAGGCAAAAT GCCGCAAAAA AGGGAATAAG GGCGACACGG
       GTTTTTGTCC TTCCGTTTTA CGGCGTTTTT TCCCTTATTC CCGCTGTGCC

1351   AAATGTTGAA TACTCATACT CTTCCTTTTT CAATATTATT GAAGCATTTA
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
          TTTACAACTT ATGAGTATGA GAAGGAAAAA GTTATAATAA CTTCGTAAAT

                                                       BsrGI
                                                      ~~~~~~~~
   1401   TCAGGGTTAT TGTCTCATGA GCGGATACAT ATTTGAATGT ACATGAAATT
          AGTCCCAATA ACAGAGTACT CGCCTATGTA TAAACTTACA TGTACTTTAA

   1451   GTAAACGTTA ATATTTTGTT AAAATTCGCG TTAAATTTTT GTTAAATCAG
          CATTTGCAAT TATAAAACAA TTTTAAGCGC AATTTAAAAA CAATTTAGTC

   1501   CTCATTTTTT AACCAATAGG CCGAAATCGG CAAAATCCCT TATAAATCAA
          GAGTAAAAAA TTGGTTATCC GGCTTTAGCC GTTTTAGGGA ATATTTAGTT

   1551   AAGAATAGAC CGAGATAGGG TTGAGTGTTG TTCCAGTTTG GAACAAGAGT
          TTCTTATCTG GCTCTATCCC AACTCACAAC AAGGTCAAAC CTTGTTCTCA

   1601   CCACTATTAA AGAACGTGGA CTCCAACGTC AAAGGGCGAA AAACCGTCTA
          GGTGATAATT TCTTGCACCT GAGGTTGCAG TTTCCCGCTT TTTGGCAGAT

   1651   TCAGGGCGAT GGCCCACTAC GAGAACCATC ACCCTAATCA AGTTTTTTGG
          AGTCCCGCTA CCGGGTGATG CTCTTGGTAG TGGGATTAGT TCAAAAAACC

                                                         BanII
                                                        ~~~~~~~
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
1701  GGTCGAGGTG CCGTAAAGCA CTAAATCGGA ACCCTAAAGG GAGCCCCCGA
      CCAGCTCCAC GGCATTTCGT GATTTAGCCT TGGGATTTCC CTCGGGGGCT

1751  TTTAGAGCTT GACGGGGAAA GCCGGCGAAC GTGGCGAGAA AGGAAGGGAA
      AAATCTCGAA CTGCCCCTTT CGGCCGCTTG CACCGCTCTT TCCTTCCCTT

1801  GAAAGCGAAA GGAGCGGGCG CTAGGGCGCT GGCAAGTGTA GCGGTCACGC
      CTTTCGCTTT CCTCGCCCGC GATCCCGCGA CCGTTCACAT CGCCAGTGCG

1851  TGCGCGTAAC CACCACACCC GCCGCGCTTA ATGCGCCGCT ACAGGGCGCG
      ACGCGCATTG GTGGTGTGGG CGGCGCGAAT TACGCGGCGA TGTCCCGCGC

        NheI
       ~~~~~~
1901  TGCTAGCGGA GTGTATACTG GCTTACTATG TTGGCACTGA TGAGGGTGTC
      ACGATCGCCT CACATATGAC CGAATGATAC AACCGTGACT ACTCCCACAG

            XmnI                                  AgeI
        ~~~~~~~~~~~                             ~~~~~~~
1951  AGTGAAGTGC TTCATGTGGC AGGAGAAAAA AGGCTGCACC GGTGCGTCAG
      TCACTTCACG AAGTACACCG TCCTCTTTTT TCCGACGTGG CCACGCAGTC

2001  CAGAATATGT GATACAGGAT ATATTCCGCT TCCTCGCTCA CTGACTCGCT
      GTCTTATACA CTATGTCCTA TATAAGGCGA AGGAGCGAGT GACTGAGCGA
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
2051   ACGCTCGGTC GTTCGACTGC GGCGAGCGGA AATGGCTTAC GAACGGGGCG
       TGCGAGCCAG CAAGCTGACG CCGCTCGCCT TTACCGAATG CTTGCCCCGC

2101   GAGATTTCCT GGAAGATGCC AGGAAGATAC TTAACAGGGA AGTGAGAGGG
       CTCTAAAGGA CCTTCTACGG TCCTTCTATG AATTGTCCCT TCACTCTCCC

2151   CCGCGGCAAA GCCGTTTTTC CATAGGCTCC GCCCCCCTGA CAAGCATCAC
       GGCGCCGTTT CGGCAAAAAG GTATCCGAGG CGGGGGGACT GTTCGTAGTG

2201   GAAATCTGAC GCTCAAATCA GTGGTGGCGA AACCCGACAG GACTATAAAG
       CTTTAGACTG CGAGTTTAGT CACCACCGCT TTGGGCTGTC CTGATATTTC

2251   ATACCAGGCG TTTCCCCCTG GCGGCTCCCT CCTGCGCTCT CCTGTTCCTG
       TATGGTCCGC AAAGGGGGAC CGCCGAGGGA GGACGCGAGA GGACAAGGAC

                   AgeI
                 ~~~~~~~
2301   CCTTTCGGTT TACCGGTGTC ATTCCGCTGT TATGGCCGCG TTTGTCTCAT
       GGAAAGCCAA ATGGCCACAG TAAGGCGACA ATACCGGCGC AAACAGAGTA

2351   TCCACGCCTG ACACTCAGTT CCGGGTAGGC AGTTCGCTCC AAGCTGGACT
       AGGTGCGGAC TGTGAGTCAA GGCCCATCCG TCAAGCGAGG TTCGACCTGA
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
2401   GTATGCACGA ACCCCCCGTT CAGTCCGACC GCTGCGCCTT ATCCGGTAAC
       CATACGTGCT TGGGGGGCAA GTCAGGCTGG CGACGCGGAA TAGGCCATTG

2451   TATCGTCTTG AGTCCAACCC GGAAAGACAT GCAAAAGCAC CACTGGCAGC
       ATAGCAGAAC TCAGGTTGGG CCTTTCTGTA CGTTTTCGTG GTGACCGTCG

2501   AGCCACTGGT AATTGATTTA GAGGAGTTAG TCTTGAAGTC ATGCGCCGGT
       TCGGTGACCA TTAACTAAAT CTCCTCAATC AGAACTTCAG TACGCGGCCA

2551   TAAGGCTAAA CTGAAAGGAC AAGTTTTAGT GACTGCGCTC CTCCAAGCCA
       ATTCCGATTT GACTTTCCTG TTCAAAATCA CTGACGCGAG GAGGTTCGGT

2601   GTTACCTCGG TTCAAAGAGT TGGTAGCTCA GAGAACCTAC GAAAAACCGC
       CAATGGAGCC AAGTTTCTCA ACCATCGAGT CTCTTGGATG CTTTTTGGCG

2651   CCTGCAAGGC GGTTTTTTCG TTTTCAGAGC AAGAGATTAC GCGCAGACCA
       GGACGTTCCG CCAAAAAAGC AAAAGTCTCG TTCTCTAATG CGCGTCTGGT

                                  BglII

2701   AAACGATCTC AAGAAGATCA TCTTATTA
       TTTGCTAGAG TTCTTCTAGT AGAATAAT
```

Figure 35b: List of oligonucleotides used for synthesis of modules

M1: PCR using template

NoVspAatII: TAGACGTC

M2: synthesis

BloxA-A: TATGAGATCTCATAACTTCGTATAATGTACGCTATACG-AAGTTAT

BloxA-B: TAATAACTTCGTATAGCATACATTATACGAAGTTATG-AGATCTCA

M3: PCR, NoVspAatII as second oligo

XloxS-muta: CATTTTTTGCCCTCGTTATCTACGCATGCGATAACTTCGTA-TAGCGTACATTATACGAAGTTATTCTAGACATGGTCATAGCTGTTTCCTG

M7-I: PCR

gIIINEW-fow: GGGGGGAATTCGGTGGTGGTGGATCTGCGTGCGCTG-AAACGGTTGAAAGTTG

gIIINEW-rev: CCCCCCCAAGCTTATCAAGACTCCTTATTACG

M7-II: PCR

gIIIss-fow: GGGGGGGGAATTCGGAGGCGGTTCCGGTGGTGGC

M7-III: PCR

gIIIsupernew-fow: GGGGGGGGAATTCGAGCAGAAGCTGATCTCT-GAGGAGGATCTGTAGGGTGGTGGCTCTGGTTCCGGTGATTTTG

Figure 35b: List of oligonucleotides used for synthesis of modules (continued)

M8: synthesis

lox514-A: CCATAACTTCGTATAATGTACGCTATACGAAGTTATA

lox514-B: AGCTTATAACTTCGTATAGCGTACATTATACGAAGT-TATGGCATG

M9II: synthesis

M9II-fow: AGCTTGACCTGTGAAGTGAAAAATGGCGCAGATT-GTGCGACATTTTTTTTGTCTGCCGTTTAATTAAAGGGGGGGT

M9II-rev: GTACACCCCCCCCAGGCCGGCCCCCCCCCCCTTTAA-TTAAACGGCAGACAAAAAAAATGTCGCACAATCTGCG

M10II: assembly PCR with template

bla-fow: GGGGGGGTGTACATTCAAATATGTATCCGCTCATG

bla-seq4: GGGTTACATCGAACTGGATCTC

bla1-muta: CCAGTTCGATGTAACCCACTCGCGCACCCAACTGATC-CTCAGCATCTTTTACTTTCACC

blaII-muta: ACTCTAGCTTCCCGGCAACAGTTAATAGACTGGATG-GAGGCGG

bla-NEW: CTGTTGCCGGGAAGCTAGAGTAAG

bla-rev: CCCCCCCTTAATTAAGGGGGGGGCCGGCCATTATCAAA-AAGGATCTCAAGAAGATCC

M11II/III: PCR, site-directed mutagenesis

Figure 35b: List of oligonucleotides used for synthesis of modules (continued)

f1-fow: GGGGGGGCTAGCACGCGCCCTGTAGCGGCGCATTAA

f1-rev: CCCCCCCTGTACATGAAATTGTAAACGTTAATATTTTG

f1-t133.muta: GGGCGATGGCCCACTACGAGAACCATCACCCTAATC

M12: assembly PCR using template

p15-fow: GGGGGAGATCTAATAAGATGATCTTCTTGAG

p15-NEWI: GAGTTGGTAGCTCAGAGAACCTACGAAAAACCGCCCTG-CAAGGCG

p15-NEWII: GTAGGTTCTCTGAGCTACCAACTC

p15-NEWIII: GTTTCCCCCTGGCGGCTCCCTCCTGCGCTCTCCTGTTCCT-GCC

p15-NEWIV: AGGAGGGAGCCGCCAGGGGGAAAC

p15-rev: GACATCAGCGCTAGCGGAGTGTATAC

M13: synthesis

BloxXB-A: GATCTCATAACTTCGTATAATGTATGCTATACGAAGTTA-TTCA

BloxXB-B: GATCTGAATAACTTCGTATAGCATACATTATACGAAGTTA-TGAGA

M14-Ext2: PCR, site-directed mutagenesis

ColEXT2-fow: GGGGGGAGATCTGACCAAAATCCCTTAACGTGAG

Col-mutaI: GGTATCTGCGCTCTGCTGTAGCCAGTTACCTTCGG

Figure 35b: List of oligonucleotides used for synthesis of modules (continued)

Col-rev: CCCCCCCGCTAGCCATGTGAGCAAAAGGCCAGCAA

M17: assembly PCR using template

CAT-1: GGGACGTCGGGTGAGGTTCCAAC

CAT-2: CCATACGGAACTCCGGGTGAGCATTCATC

CAT-3: CCGGAGTTCCGTATGG

CAT-4: ACGTTTAAATCAAAACTGG

CAT-5: CCAGTTTTGATTTAAACGTAGCCAATATGGACAACTTCTTC-GCCCCCGTTTTCACTATGGGCAAATATT

CAT-6: GGAAGATCTAGCACCAGGCGTTTAAG

M41: assembly PCR using template

LAC1: GAGGCCGGCCATCGAATGGCGCAAAAC

LAC2: CGCGTACCGTCCTCATGGGAGAAAATAATAC

LAC3: CCATGAGGACGGTACGCGACTGGGCGTGGAGCATCTGGTCGCA-TTGGGTCACCAGCAAATCCGCTGTTAGCTGGCCCATTAAG

LAC4: GTCAGCGGCGGGATATAACATGAGCTGTCCTCGGTATCGTCG

LAC5: GTTATATCCCGCCGCTGACCACCATCAAAC

LAC6: CATCAGTGAATCGGCCAACGCGCGGGGAGAGGCGGTTTGCGT4TTG-GGAGCCAGGGTGGTTTTTC

LAC7: GGTTAATTAACCTCACTGCCCGCTTTCCAGTCGGGAAACCTGTCGTGCC-AGCTGCATCAGTGAATCGGCCAAC

M41-MCS-fow: CTAGACTAGTGTTTAAACCGGACCGGGGGGGGGCTT-AAGGGGGGGGGGG

Figure 35b: List of oligonucleotides used for synthesis of modules (continued)

M41-MCS-rev: CTAGCCCCCCCCCCCCTTAAGCCCCCCCCCGGTCCGGT-TTAAACACTAGT

M41-fow: CTAGACTAGTGTTTAAACCGGACCGGGGGGGGGCTTAA-GGGGGGGGGGG

M41-rev: CCCCCCCTTAAGTGGGCTGCAAAACAAAACGGCCTCC-TGTCAGGAAGCCGCTTTTATCGGGTAGCCTCACTGCCCGCTTTCC

M41-A2: GTTGTTGTGCCACGCGGTTAGGAATGTAATTCAGCTCCGC

M41-B1: AACCGCGTGGCACAACAAC

M41-B2: CTTCGTTCTACCATCGACACGACCACGCTGGCACCCAGTTG

M41-C1: GTGTCGATGGTAGAACGAAG

M41-CII: CCACAGCAATAGCATCCTGGTCATCCAGCGGATAGTT-AATAATCAGCCCACTGACACGTTGCGCGAG

M41-DI: GACCAGGATGCTATTGCTGTGG

M41-DII: CAGCGCGATTTGCTGGTGGCCCAATGCGACCAGATGC

M41-EI: CACCAGCAAATCGCGCTG

M41-EII: CCCGGACTCGGTAATGGCACGCATTGCGCCCAGCGCC

M41-FI: GCCATTACCGAGTCCGGG

M42: synthesis

Eco-H5-Hind-fow: AATTCCACCATCATCACCATTGACGTCTA

Eco-H5-Hind-rev: AGCTTAGACGTCAATGGTGATGATGGTGG

Figure 36: functional map and sequence of ß-lactamase-MCS module

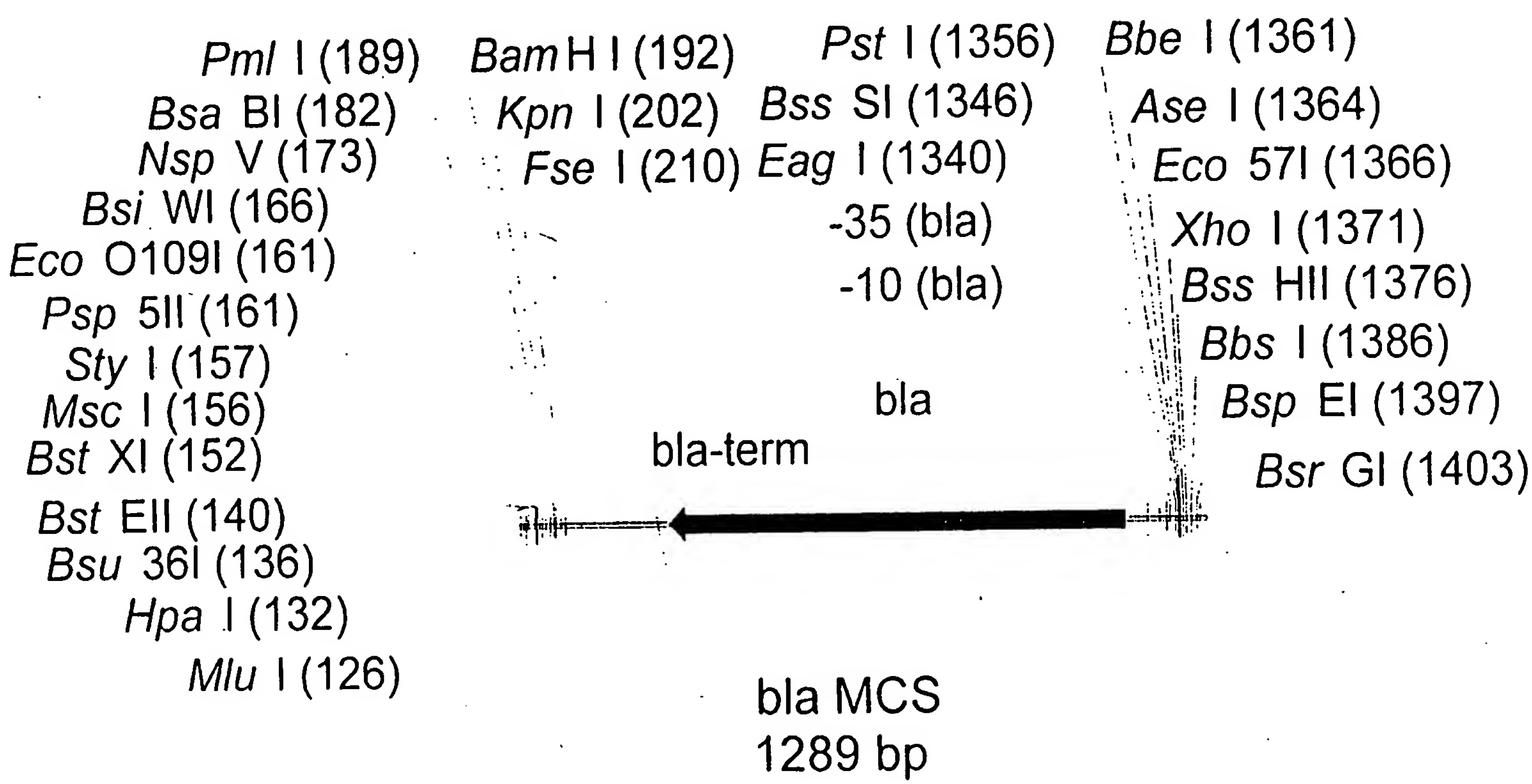


Figure 36: functional map and sequence of ß-lactamase-MCS module (continued)

```
                                            StyI
                                            ~~~~~~~
                                              Psp5II
                                              ~~~~~~~~
      MluI    Bsu36I           BstXI         Eco0109I
      ~~~~~   ~~~~~~~~~   ~~~~~~~~~~~~~~~    ~~~~~~~~
         HpaI      BstEII            MscI             BsiWI NspV
         ~~~~~~~   ~~~~~~~~          ~~~~~~~~      ~~~~~~~~~~~~~~
126   CGCGTTAACC TCAGGTGACC AAGCCCCTGG CCAAGGTCCC GTACGTTCGA
      GCGCAATTGG AGTCCACTGG TTCGGGGACC GGTTCCAGGG CATGCAAGCT

                  PmlI
                 ~~~~~~~
      NspVBsaBI        BamHI   KpnI       FseI
      ~~~~~~~~~~~~~   ~~~~~~~~~~~~~~~ ~~~~~~~~~~
176   AGATTACCAT CACGTGGATC CGGTACCAGG CCGGCCATTA TCAAAAAGGA
      TCTAATGGTA GTGCACCTAG GCCATGGTCC GGCCGGTAAT AGTTTTTCCT

226   TCTCAAGAAG ATCCTTTGAT CTTTTCTACG GGGTCTGACG CTCAGTGGAA
      AGAGTTCTTC TAGGAAACTA GAAAAGATGC CCCAGACTGC GAGTCACCTT

276   CGAAAACTCA CGTTAAGGGA TTTTGGTCAT GAGATTATCA AAAAGGATCT
      GCTTTTGAGT GCAATTCCCT AAAACCAGTA CTCTAATAGT TTTTCCTAGA
```

Figure 36: functional map and sequence of ß-lactamase-MCS module (continued)

```
326  TCACCTAGAT CCTTTTAAAT TAAAAATGAA GTTTTAAATC AATCTAAAGT
     AGTGGATCTA GGAAAATTTA ATTTTTACTT CAAAATTTAG TTAGATTTCA

376  ATATATGAGT AAACTTGGTC TGACAGTTAC CAATGCTTAA TCAGTGAGGC
     TATATACTCA TTTGAACCAG ACTGTCAATG GTTACGAATT AGTCACTCCG

426  ACCTATCTCA GCGATCTGTC TATTTCGTTC ATCCATAGTT GCCTGACTCC
     TGGATAGAGT CGCTAGACAG ATAAAGCAAG TAGGTATCAA CGGACTGAGG

476  CCGTCGTGTA GATAACTACG ATACGGGAGG GCTTACCATC TGGCCCCAGT
     GGCAGCACAT CTATTGATGC TATGCCCTCC CGAATGGTAG ACCGGGGTCA

526  GCTGCAATGA TACCGCGAGA CCCACGCTCA CCGGCTCCAG ATTTATCAGC
     CGACGTTACT ATGGCGCTCT GGGTGCGAGT GGCCGAGGTC TAAATAGTCG

576  AATAAACCAG CCAGCCGGAA GGGCCGAGCG CAGAAGTGGT CCTGCAACTT
     TTATTTGGTC GGTCGGCCTT CCCGGCTCGC GTCTTCACCA GGACGTTGAA

626  TATCCGCCTC CATCCAGTCT ATTAACTGTT GCCGGGAAGC TAGAGTAAGT
     ATAGGCGGAG GTAGGTCAGA TAATTGACAA CGGCCCTTCG ATCTCATTCA

676  AGTTCGCCAG TTAATAGTTT GCGCAACGTT GTTGCCATTG CTACAGGCAT
     TCAAGCGGTC AATTATCAAA CGCGTTGCAA CAACGGTAAC GATGTCCGTA
```

Figure 36: functional map and sequence of ß-lactamase-MCS module (continued)

```
726   CGTGGTGTCA CGCTCGTCGT TTGGTATGGC TTCATTCAGC TCCGGTTCCC
      GCACCACAGT GCGAGCAGCA AACCATACCG AAGTAAGTCG AGGCCAAGGG

776   AACGATCAAG GCGAGTTACA TGATCCCCCA TGTTGTGCAA AAAAGCGGTT
      TTGCTAGTTC CGCTCAATGT ACTAGGGGGT ACAACACGTT TTTTCGCCAA

826   AGCTCCTTCG GTCCTCCGAT CGTTGTCAGA AGTAAGTTGG CCGCAGTGTT
      TCGAGGAAGC CAGGAGGCTA GCAACAGTCT TCATTCAACC GGCGTCACAA

876   ATCACTCATG GTTATGGCAG CACTGCATAA TTCTCTTACT GTCATGCCAT
      TAGTGAGTAC CAATACCGTC GTGACGTATT AAGAGAATGA CAGTACGGTA

926   CCGTAAGATG CTTTTCTGTG ACTGGTGAGT ACTCAACCAA GTCATTCTGA
      GGCATTCTAC GAAAAGACAC TGACCACTCA TGAGTTGGTT CAGTAAGACT

976   GAATAGTGTA TGCGGCGACC GAGTTGCTCT TGCCCGGCGT CAATACGGGA
      CTTATCACAT ACGCCGCTGG CTCAACGAGA ACGGGCCGCA GTTATGCCCT

1026  TAATACCGCG CCACATAGCA GAACTTTAAA AGTGCTCATC ATTGGAAAAC
      ATTATGGCGC GGTGTATCGT CTTGAAATTT TCACGAGTAG TAACCTTTTG

1076  GTTCTTCGGG GCGAAAACTC TCAAGGATCT TACCGCTGTT GAGATCCAGT
      CAAGAAGCCC CGCTTTTGAG AGTTCCTAGA ATGGCGACAA CTCTAGGTCA
```

Figure 36: functional map and sequence of ß-lactamase-MCS module (continued)

```
1126   TCGATGTAAC CCACTCGTGC ACCCAACTGA TCTTCAGCAT CTTTTACTTT
       AGCTACATTG GGTGAGCACG TGGGTTGACT AGAAGTCGTA GAAAATGAAA
                    BssSI                Eco57I
                   ~~~~~~~               ~~~~~~~

1176   CACCAGCGTT TCTGGGTGAG CAAAAACAGG AAGGCAAAAT GCCGCAAAAA
       GTGGTCGCAA AGACCCACTC GTTTTTGTCC TTCCGTTTTA CGGCGTTTTT

1226   AGGGAATAAG GGCGACACGG AAATGTTGAA TACTCATACT CTTCCTTTTT
       TCCCTTATTC CCGCTGTGCC TTTACAACTT ATGAGTATGA GAAGGAAAAA

1276   CAATATTATT GAAGCATTTA TCAGGGTTAT TGTCTCATGA GCGGATACAT
       GTTATAATAA CTTCGTAAAT AGTCCCAATA ACAGAGTACT CGCCTATGTA

                                   PstI                 XhoI
                                 ~~~~~~~~              ~~~~~~~
                    EagI     BssSI           BbeI   AseI    BssHII
                   ~~~~~~~~~~~~~~~          ~~~~~~~~~~~~~~~      ~
1326   ATTTGAATGT ACTCGGCCGC ACGAGCTGCA GGCGCCATTA ATGGCTCGAG
       TAAACTTACA TGAGCCGGCG TGCTCGACGT CCGCGGTAAT TACCGAGCTC

       BssHII                  BspEI BsrGI
       ~~~~~                  ~~~~~~~~~~~~~~~
```

Figure 36: functional map and sequence of ß-lactamase-MCS module (continued)

```
1376   CGCGCTTCAG CGCTTTGTCT TCCGGATGTA CATGAAATT
       GCGCGAAGTC GCGAAACAGA AGGCCTACAT GTACTTTAA
           Eco57I         BbsI
           ~~~~~~~      ~~~~~~~~
```

Figure 37: Oligo and primer design for Vκ CDR3 libraries

		1									10									
O_K3L_5	5'-	G	C	C	C	T	G	C	A	A	G	C	G	G	A	A	G	A	C	
														BbsI						
														E			D			
Vk1 & Vk3	5'-	G	C	C	C	T	G	C	A	A	G	C	G	G	A	A	G	A	C	
														E			D			
Vk2	5'-	G	C	C	C	T	G	C	A	A	G	C	G	G	A	A	G	A	C	
														E			D			
Vk4	5'-	G	C	C	C	T	G	C	A	A	G	C	G	G	A	A	G	A	C	

Figure 37: Oligo and primer design for Vκ CDR3 libraries

20 30 40

-3'

F A T/V Y Y C Q
T T T G C G A C T T A T T A T T G C C A
G T T

V G V Y Y C
G T G G G C G T G T A T T A T T G C C A

V A V Y Y C
G T G G C G G T G T A T T A T T G C C A

A	
C	
D	
E	
F	T T T
G	
H	C A T
I	
K	
L	C T T
M	A T G
N	
P	
Q	C A G
R	
S	
T	
V	
W	
Y	
	80% Q

Figure 37: Oligo and primer design for Vκ CDR3 libraries

50 60

3'- G G A

T
G A C C T

T
G A C C T

T
G A C C T

G C T			G C T		G C T
G A T	G A T	G A T	G A T		G A T
G A G			G A G		G A G
T T T			T T T		T T T
G G T	G G T	G G T	G G T		G G T
C A T			C A T		C A T
A T T			A T T		A T T
A A G			A A G		A A G
C T T			C T T		C T T
A T G			A T G		A T G
A A T	A A T	A A T	A A T		A A T
			C C T	C C T	C C T
C A G			C A G		C A G
C G T			C G T		C G T
T C T	T C T	T C T	T C T	T C T	T C T
A C T			A C T		A C T
G T T			G T T		G T T
T G G			T G G		T G G
T A T	T A T		T A T		T A T
50% Y				80% P	

Figure 37: Oligo and primer design for Vκ CDR3 libraries

```
          70                      80 81
A A C C G G T A A G C T T T C G  G  -5' O_K3L_3
 [   MscI    ]
F    G      Q
T [T G G C C A] T T C G A A A G C  C  -3'

F    G      Q
T [T G G C C A] T T C G A A A G C  C  -3'
F    G      Q
T [T G G C C A] T T C G A A A G C  C  -3'
```

Figure 38: Oligo and primer design for Vλ CDR3 libraries

```
    1                  10                  20
                          E     D     E     A     D
5'- C C T G C A A G C G G A A G A C G A A G C G G A T T -
```

Figure 38: Oligo and primer design for Vλ CDR3 libraries

30 40 50

Y Y C Q S D

-ATTATTGCCAGAGC GAC

A			GCT	GCT -
C				
D			GAT	GAT
E			GAG	GAG
F			TTT	TTT
G			GGT	GGT
H			CAT	CAT
I			ATT	ATT
K			AAG	AAG
L			CTT	CTT
M			ATG	ATG
N			AAT	AAT
P			CCT	CCT
Q			CAG	CAG
R	CGT		CGT	CGT
S			TCT	TCT
T			ACT	ACT
V			GTT	GTT
W	TGG			
Y	TAT		TAT	TAT
	3	1	18	18
	3	1	18	18
	3	1	18	18

Figure 38: Oligo and primer design for Vλ CDR3 libraries

60 70 80

G G G T K L

GGCGGCGGCACGAAGTTA

		gap	gap		
-	GCT	GCT	GCT	GCT	
	GAT	GAT	GAT	GAT	
	GAG	GAG	GAG	GAG	
	TTT	TTT	TTT	TTT	
	GGT	GGT	GGT	GGT	
	CAT	CAT	CAT	CAT	
	ATT	ATT	ATT	ATT	
	AAG	AAG	AAG	AAG	
	CTT	CTT	CTT	CTT	
	ATG	ATG	ATG	ATG	
	AAT	AAT	AAT	AAT	
	CCT	CCT	CCT	CCT	
	CAG	CAG	CAG	CAG	
	CGT	CGT	CGT	CGT	
	TCT	TCT	TCT	TCT	
	ACT	ACT	ACT	ACT	
	GTT	GTT	GTT	GTT	
				TGG	
	TAT	TAT	TAT	TAT	Variability
	18			19	3.32E+05
	18	18		19	5.98E+06
	18	18	18	19	1.08E+08

Figure 38: Oligo and primer design for Vλ CDR3 libraries

```
             90              100          108
 T    V    L    G    Q    E    F
ACCGTTCTTGGCCAG[GAATTC]GAGCC-3'
            3'-CCGGTCCTTAAGCTCGG-5'
```

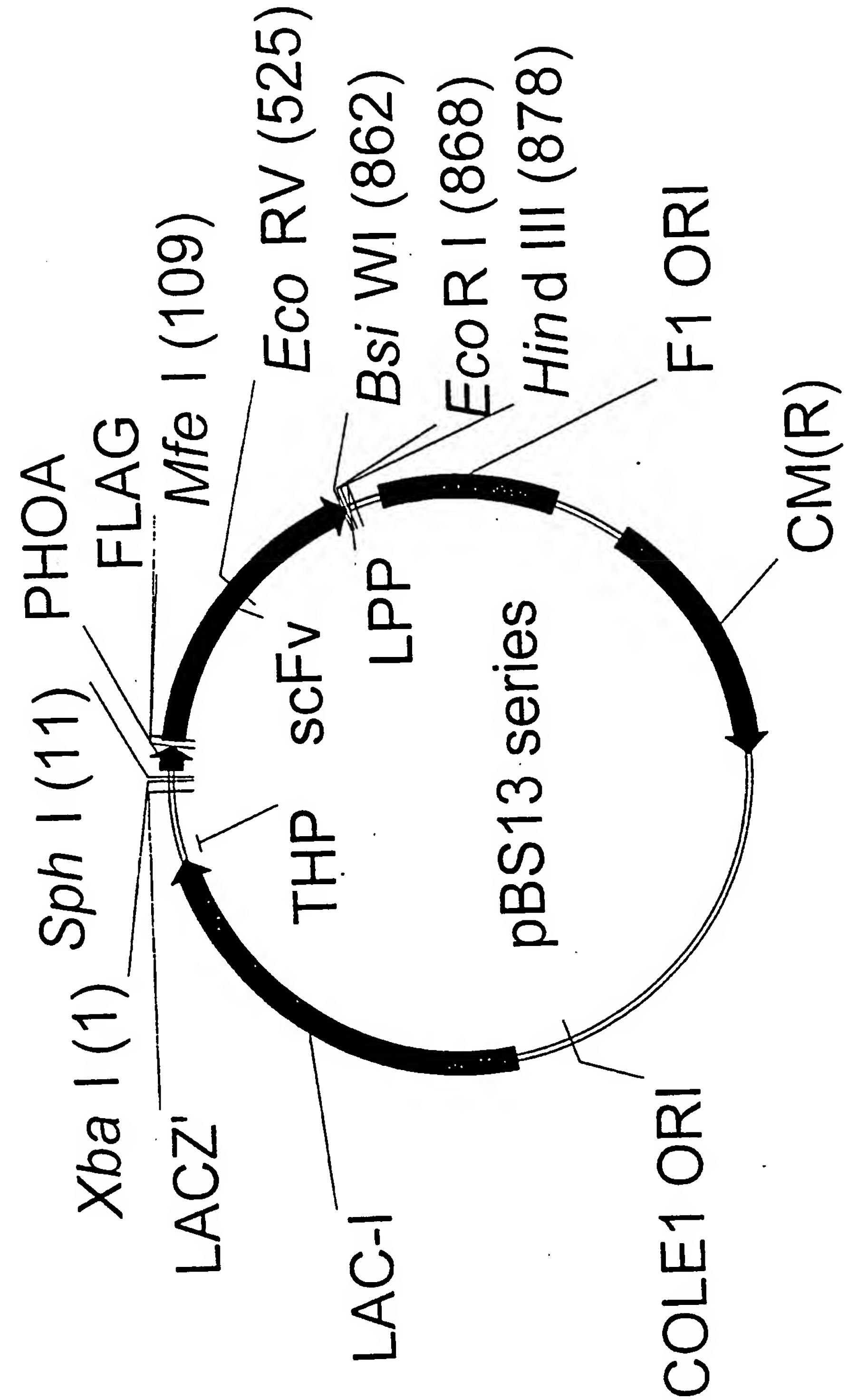


Figure 39: functional map of expression vector series pBS13

Figure 40: Expression data for HuCAL scFvs (pBS13, 30°C)

% soluble	κ1	κ2	κ3	κ4	λ1	λ2	λ3
H1A	61%	58%	52%	42%	90%	61%	60%
H1B	39%	48%	66%	48%	47%	39%	36%
H2	47%	57%	46%	49%	37%	36%	45%
H3	85%	67%	76%	61%	80%	71%	83%
H4	69%	52%	51%	44%	45%	33%	42%
H5	49%	49%	46%	67%	54%	46%	47%
H6	90%	58%	54%	47%	45%	50%	51%

Total amount compared to H3κ2	κ1	κ2	κ3	κ4	λ1	λ2	λ3
H1A	289%	94%	166%	272%	20%	150%	78%
H1B	219%	122%	89%	139%	117%	158%	101%
H2	186%	223%	208%	182%	126%	60%	97%
H3	50%		71%	54%	59%	130%	47%
H4	37%	55%	60%	77%	195%	107%	251%
H5	98%	201%	167%	83%	93%	128%	115%
H6	65%	117%	89%	109%	299%	215%	278%

Figure 40: Expression data for HuCAL scFvs (pBS13, 30°C)

Soluble amount compared to H3κ2	κ1	κ2	κ3	κ4	λ1	λ2	λ3
H1A	191%	88%	121%	122%	26%	211%	76%
H1B	124%	95%	83%	107%	79%	142%	59%
H2	126%	204%	139%	130%	66%	50%	70%
H3	63%	-	81%	49%	69%	143%	61%
H4	40%	47%	49%	54%	95%	55%	125%
H5	69%	158%	116%	80%	72%	84%	84%
H6	85%	122%	87%	77%	162%	162%	212%

	McPC
soluble	38%
%H3k2 total	117%
%H3k2 soluble	69%

INTERNATIONAL SEARCH REPORT

Inv ·onal Application No
PCT/EP 96/03647

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/13 C12N15/10 C12N15/62 C12N15/70 C12N1/21
C07K1/04 G01N33/53

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	EUROPEAN J. IMMUNOLOGY, vol. 23, July 1993, VCH VERLAGSGESELLSCHAFT MBH, WEINHEIM, BRD, pages 1456-1461, XP000616572 S.C. WILLIAMS AND G. WINTER: "Cloning and sequencing of human immunoglobulin V-lambda gene segments" cited in the application see the whole document --- -/--	1-55

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
30 January 1997	11.02.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hornig, H

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PROC. NATL.ACAD SCI., vol. 89, May 1992, NATL. ACAD SCI.,WASHINGTON,DC,US;, pages 4457-4461, XP002024223 C. F. BARBAS III ET AL.: "Semisynthetic combinatorial antibody libraries: a chemical solution to the diversity problem" cited in the application see the whole document ---	1-55
A	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 89, no. 21, 1 November 1992, pages 10026-10030, XP000322464 COLLET T A ET AL: "A BINARY PLASMID SYSTEM FOR SHUFFLING COMBINATORIAL ANTIBODY LIBRARIES" see the whole document ---	1-55
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-/--

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A	WO 95 11998 A (UNITED BIOMEDICAL INC) 4 May 1995 see the whole document ---	1-55
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PCT/EP 96/03647

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		CA-A- 2002868	11-05-90
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		ES-T- 2052027	01-07-94
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WO-A-9511998	04-05-95	AU-A- 8091694	22-05-95
		EP-A- 0725838	14-08-96

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Information on patent family members

Int onal Application No
PCT/EP 96/03647

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CA-A- 2002868	11-05-90
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		DE-T- 68913658	08-09-94
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